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COLLEGE OF MEDICINE AND HEALTH SCIENCE

INSTITUTE OF PUBLIC HEALTH

Incidence And determinants for vascular complications among type II diabetes mellitus patients In university Of Gondar referral hospital: A retrospective follow-up study.

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ACRONYMS

AHR	Adjusted Hazard Ratio
AIC	Akaike's Information Criteria
BIC	Bayesian Information Criteria
BP	Blood Pressure
CHD	Coronary Heart Diseases
CHR	Crud Hazard Ratio
CKD	Chronic Kidney Diseases
CVD	Cardiovascular Diseases
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
FBS	Fasting Blood Sugar
HDL-C	High Density Lipoprotein Cholesterol
HR	Hazard Raito
HTN	Hypertension
IQR	Inter Quartile Range
LDL-C	Low Density Lipoprotein cholesterol
PAD	Peripheral Arterial Disease
PH	Proportional Hazard
OHA	Oral Hypoglycemic Agents
SBP	Systolic Blood Pressure
SD	Standard Deviation

ABSTRACT

Introduction: Type II Diabetes Mellitus is a serious metabolic disease in the world and it is highly associated with an increased risk of vascular complication. There are 1.9 million people living with Diabetes in Ethiopia and DM is found to be the ninth leading cause of death due to its complications. Even though the rate of vascular complications is increasing there is limited updated information about the problem. Hence this study was designed to investigate vascular complications and its determinates.

Objective: The aim of this study was to estimate the Incidence and identify determinates for vascular complication among type II diabetes mellitus patients in university of Gondar referral hospital.

Methodology: Institution based Retrospective follow-up study was conducted at University of Gondar referral hospital among 364 patients who were newly diagnosed as having type II DM from September 2005 up to August 2012. Simple random sampling technique was used to select these patients and they were followed retrospectively up to March 2017. The data was entered in to EPI info version 7.0 and transferred to STATA version 14.1 for analysis. Both bi-variable and multi variable Cox regression (parametric and semi-parametric) models were fitted to identify the risk factors. The best model was selected by using AIC, BIC and log likelihood criteria. 95% confidence interval of hazard ratio (HR) was computed and variables having p - value less than 0.05 in the multivariable model were considered to be significantly associated with the dependent variable.

Result: A total of 341 were followed retrospectively for a median follow up time of 81.50 months (IQR=36.07 months). Out of all 97(28%) vascular complications was observed with an incidence rate of 33.81 cases/ 10000 person month observation. The cumulative probability of vascular complications was 0.8617 in a total of 28692.8 person month observations. Male sex (AHR= 0.50, 95%: 0.27, 0.94), having hypertension at baseline(AHR= 3.99, 95%CI: 1.87, 8.56), , positive protein urea (AHR= 1.69, 95%CI: 1.03, 2.78), HDL-C level ≥40mg/dl (AHR= 0.43, 95%CI: 0.24, 0.77), LDL-C level >100mg/dl (AHR= 3.05, 95%CI: 1.47, 6.35) and Triglyceride >150mg/dl (AHR= 2.74, 95%CI: 1.28, 5.84) were found to be significantly associated with vascular complication**.**

Conclusion: The incidence of vascular complication was relatively low. Hypertension at baseline, LDL-C>100mg/dl, triglyceride >150mg/dl, HDL≥40 mg/dl and male sex were significant predictors of vascular complication. Hence close monitoring of patients with hypertension co morbidity and deslipedemia should be considered.

Key words: Incidence, Vascular complication, Type II DM, University of Gondar referral hospital.

1. INTRODUCTION

1.1 Statement of the problem

Diabetes mellitus is a chronic metabolic disorder characterized by chronic hyperglycemia and it is classified in to four major groups that are type I, type II, gestational diabetes and specific types of DM (1). Type II DM a serious metabolic diseases in the world and it is highly associated with vascular complications(2). Vascular complications caused by Type II DM include neuropathy, nephropathy, retinopathy, coronary heart dieses, peripheral arterial diseases and stroke (3).

Globally, the prevalence of DM is 8.5 % and it is estimated one adult in 10 will have diabetes in the world by 2035 (4). Sub Saharan Africa countries are expected to experience the worldwide fastest increase in the number of people living with type 2 diabetes (141 %) in the next two decades (2). Ethiopia is the third most populous country from Africa with 1.9 million people living with diabetes (2, 5)

The seriousness of diabetes is largely a result of its associated vascular complications, which can be disabling and even fatal. In 2012 there were 1.5 million deaths worldwide directly caused by diabetes and its complications and It was the eighth leading cause of death among both sexes and the fifth leading cause of death in women. Globally the proportion of end stage renal diseases attributable to diabetes alone ranges from 12–55% and its Incidence is ten times higher among diabetics(4). Diabetic retinopathy caused 1.9% of moderate or severe visual impairment and 2.6% of blindness globally in 2010 (6). Adults with diabetes have a two or three times higher rate of cardiovascular disease like CHD, stroke and PAD than those without diabetes(7).

In Africa the age standardized mortality rate due to diabetes and its complications is estimated to be 111.3 per 100000 population (4). The prevalence of diabetic nephropathy is estimated be 6-16% in sub Saharan Africa(8) and 6.1% in Ethiopia(9) and the prevalence of retinopathy ranges from 31.4%-41.1% in Ethiopia (10). Type II diabetes is rapidly increasing non-communicable diseases and major public health challenge in developing countries like Ethiopia(11) with consequence of chronicity and pre-mature death due to its vascular complications (12, 13). In Ethiopia There were

44,655 deaths between 2012 and 2013 among people aged 20-79 due to diabetes and its associated vascular complications it is also showed that diabetes was the ninth leading cause of death in Ethiopia with 22 per 1000 death (2, 5, 14).

The most common factors affecting survival time to vascular complication of diabetes are age, sex, duration of diabetes, hypertension co morbidity(15, 16) type of treatment(17) and fasting blood sugar level (18). Ethiopian diabetics association tries to halt the increasing trends of DM and its complications by giving screening service for diabetic retinopathy by provision of free medications for the patients who cannot afford and by preparing educational sections to create awareness about the complications and how to prevent them (19).

Therefore the aim of this study was to estimate the incidence of vascular complication among type II DM patients As far as my knowledge is concerned there is limited study in this topic in the study area and we believe it will be a big input for health professionals and policy makers for prevention and risk minimization of vascular complications.

1.2 Literature review

1.2.1 Vascular complication from type II diabetes mellitus

Everyone who is diagnosed as having DM especially type II DM are at increased risk of developing Vascular complication which are classified as macro-vascular complications and micro- vascular complications. Macro-vascular are damages to the large blood vessels like peripheral arterial diseases coronary heart diseases and stork and micro vascular ones are damages to small blood vessels like neuropathy, nephropathy and retinopathy. Other possible outcomes are lost follow-up, death and being free of the complication at the end of the study.

According to a study in India the overall prevalence of micro vascular complications is found to be 30.2 % and other study in the same setting estimates the prevalence of retinopathy, nephropathy and neuropathy to be 32.5% , 30.2% , 26.8% respectively. Another study in Cameroon also shows the prevalence to be 23%, 25%, 40% respectively (20-22).

A retrospective cohort study done in Taiwan showed that 30.7% of the study participants who were free of any complication at the start of the study develop at least one complication during the study period and the most common first complications during the study are CHD, CKD and stork with a cumulative incidence after five years to be 6.8%, 4.5%, 2.9% respectively (23) According to other study in Japan that used polled data from two clinical trials the incidence of macro vascular complications like CHD, stork are found to be 5.1% and 4.1% respectively and micro vascular complications like nephropathy and retinopathy to be 3.7 % and 32% respectively after an average follow-up time of 7.2 years(16).

According to a retrospective follow up study done in Bangladesh for 13 years: patients who have developed different types of complications such as coronary heart disease, nephropathy, diabetic retinopathy, and other (PAD, stroke and foot ulcer) were 5.2%, 5.8%, 6.2%, and 10.8% respectively during their follow up period among the participants who started with no complication at the initial stage(17).

Other possible outcome for type II DM patients during the follow-up are Death and lost to follow up. A retrospective cohort study done in Asia showed 18 % and 21% of the patients were lost before and after they start treatment respectively and there is also 1% death after initiation of the treatment (24). Another retrospective follow up study conducted in Rwanda showed that the rate of lost follow up were 5.5%,11.5%,16.8% after first visit,12 months, and 24 months of follow up respectively and there were also 1.7% and 3% death after 12 and 24 months of follow-up respectively(25).

1.2.2 Factors affecting vascular complication from type 2 DM

Different studies throughout the world identified different factors associated with an increased or decreased risk of vascular complications among diabetes mellitus patients. In this section we try to bring light relevant information from relating previous studies about socio demographic, clinical and Physiologic factors that affect time to vascular complication for type 2 DM patients.

Socio demographic factors

Multiple retrospective follow up studies in Iran and Japan showed that an increased age and male sex are significantly associated with an increased risk of macro-vascular and micro vascular complications (15, 16) But according to other studies in India and Ethiopia females and older age are positively associated with an increased risk of vascular complications(18, 22). Other Meta-analysis involving 121 prospective studies showed that females are at increased risk of having vascular events(7).As the study in Bangladesh urban residents are at increased risk of having vascular complications like CHD than rural residents(17).

Clinical factors

According to a studies done in Iran Japan and India hypertension and longer duration of diabetes are highly associated with an increased risk of having both macro vascular complications like stroke, CVD and micro vascular complication like nephropathy and retinopathy (15, 16, 26). According to a study in Ireland type 2 DM patients with hypertension are at increased risk of having vascular complications (27, 28). Other studies in morocco and Cameroon also showed that having high blood pressure is

positively associated with the risk both macro and micro vascular complications specifically nephropathy and cardio vascular events (29, 30). A study conducted in Malaysia showed that patients with family history of DM have increased risk of having vascular complications(31) and other study in Zimbabwe showed for the risk of diabetic complications to be higher among obese individuals as compared to normal weight and it is also showed that higher rate of chronic complications are occurred among unemployed patients.(32)

According to a study in Bangladesh Oral hypoglycemic agents are associated with an increased risk of vascular complications like CHD and nephropathy as compared to insulin therapy(17). A study in North west pacific Among type 2 diabetes patients with an initial complication, tight glycemic control is associated with reduced risk major micro- vascular and macro vascular complication and additional complications in other organs(33, 34). A study conducted in Japan showed that Multiple insulin injections results a good glycemic control and significantly associated with a decreased risk of vascular complications(35)

Physiologic factors

According to Multi centered study that involve 28 countries from Africa, Asia and Middle east and other study in India; lipid profiles like LDL and HDL are significant predictors of vascular complications; were HDL level is negatively and LDL level is positively associated with the risk of vascular complication(26, 36) and other studies in Singapore and Zimbabwe also showed increased level of LDL(32) and low level of HDL(37) are associated with an increased risk of vascular complications and as other study in Iran Cholesterol and triglyceride level are positively associated with the risk of vascular complications(15). A study conducted in Ethiopia showed that an increased fasting plasma sugar level is significantly associated with an increased risk of micro vascular complications(18). A study conducted in India showed that an increase ether in systolic or Diastolic blood pressure and Creatinine level is positively associated with a an increased risk of vascular complication(38)

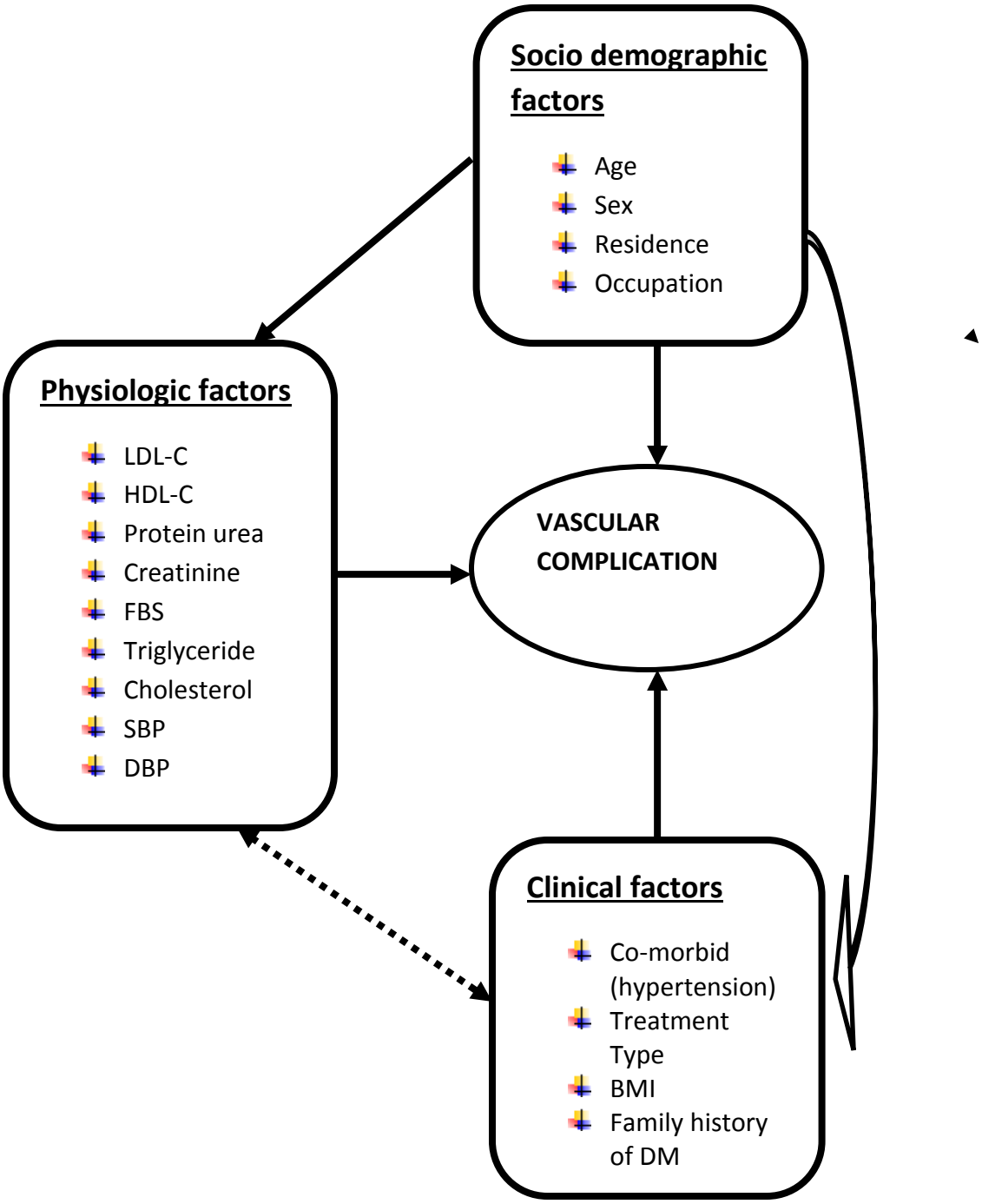

Figure 1: Conceptual frame work vascular complications from type II diabetes source- from review of literature (16-19, 27, 35, 36)

1.3 Justification of the study

Ethiopia is facing a double burden problem because Type II DM is currently increasing due to different factors such as aging, urbanization, increasing prevalence of obesity and physical inactivity and there is also an increasing trend in mortality due to its complications. However there are a limited number of updated information in Ethiopia and in the study area that documented time to vascular complication. This study have used advanced Parametric survival models to Identify significant factors that affect time to vascular complication for type II DM patients. This study could provide information for health professionals, policy makers and other governmental and none governmental organizations to maximize efforts on prevention and risk minimization of vascular complication and deaths due to the complication in the country as well as in the study area. In addition to this it could be used as a reference for other researchers.

2. OBJECTIVES

2.1 General objective

The objective of this study was to estimate the incidence and identify determinates of vascular complication among type II Diabetes mellitus patients in University of Gondar referral hospital.

2.2 Specific objective

- ✓ To estimate the incidence of vascular complication among type II Diabetes mellitus patients in University of Gondar referral hospital.
- ✓ To identify determinates for vascular complication among type II Diabetes mellitus patients in University of Gondar Hospital.

3. METHODOLOGY

3.1 Study design and period

Institution based retrospective follow up study was conducted from September 2005 up to March 2017 among type II DM patients in university of Gondar referral hospital.

3.2 Study setting

The study was conducted in University of Gondar referral hospital among type II DM patients. The hospital was established 1954 and it is located in North Gondar administrative zone, Amhara National Regional state, which is far about 750 km Northwest of Addis Ababa (the capital city of Ethiopia). According to the 2015 population projection of major cities in Ethiopia the total population size of Gondar town was estimated to be 323,900 Currently, Gondar town has one Referral Hospital and eight government Health Centers. University of Gondar Referral Hospital is a teaching Hospital which serves more than five million people of the North Gondar zone and peoples of the neighboring Zones. Around 24,552 number of people are having chronic follow-up per year and among this 8,880 are DM patients.

3.3 Source and study population

The source population for this study were type II diabetes patients having a follow up at university of Gondar referral hospital and the study population were all newly diagnosed type II diabetes patients in university of Gondar referral hospital from September 2005 to August 2012.

3.4 Inclusion and Exclusion criteria

All Newly diagnosed type II DM patients between September 2005 and August 2012 were included; however newly diagnosed patients who had any of the vascular complications at the start of the study and patients who had missing on the key variables were excluded from the study.

3.5 Sample size and sampling procedure

We have used a two step processes to determine the sample size the first one is determining the total number of expected event (vascular complications) and the second one is the total sample size required to get this number of events (vascular complications) and its given by(39).

Step 1- $M = \frac{(Z\alpha/2 + Z\beta)\text{^}2}{\Theta^2 \Pi(1-\Pi)}$

Were - *M* is number of expected events (vascular complications)

- $Z\,\alpha/2\ and\ Z\beta$ are reliability coefficients based on α and β respectively.

- *Θ* is logarithm of the hazard ratio.

- *Π* is the fraction of subjects allocated to the first group.

Step 2- $n = \frac{M}{p(event)}$

Were - *n* is the number of subjects to be followed.

M is the number of events

P is the over all probability of an event (vascular complication) at the end of the study. Therefore based on the results we found from previous retrospective follow up studies done in Asia and Ethiopia (15, 16, 18, 23) we had the following sample.

Table 1: Sample size determination

Assumptions		Predictors	Hazard ratio	Sample size(Event)
Power=80%	α=0.05	BMI (normal weight)	0.67	364(202)
Π =0.5	P(event)=0.31	Sex(Female)	1.53	262(180)
Withdrawal=10%	β=0.2	HTN(yes)	1.80	138(98)

So the sample size was **364** with the estimated number of events to be 202 and these subjects were selected based on simple random sampling from all newly diagnosed patients in the recruitment period.

3.6 Variables in the study

Dependent variable

Time to vascular complication.

Independent variables

Socio demographic- Age, Sex, Residence, Occupation

Clinical- Type of treatment, family history of DM, Hypertension, Body mass index

Physiologic factors- Low Density Lipoprotein level, High Density Lipoprotein level, Protein urea, Creatinine, Triglycerides, Cholesterol, Fasting Blood Sugar, Systolic blood pressure, Diastolic blood pressure.

3.7 Operational Definitions

Vascular complication- The first event from any of the vascular complications associated with DM like coronary heart diseases, peripheral arterial diseases, stork, retinopathy, nephropathy and neuropathy.

Censored- Includes lost to follow up, death and being event free at the end of the study.

Lost follow up- Patients not having visited the clinic at least for one year.

Time to vascular complication- The length of time in month from the start of treatment up to the development of any of the vascular complications**.**

Systolic blood pressure, Diastolic blood pressure, Creatinine, Fasting blood sugar, high density lipoprotein, low density lipoprotein, Triglyceride, total cholesterol and treatment type – The most recent measurements just before the complication or censoring time.

3.8 Data collection procedures

Data collectors: Data extraction check list was prepared in English. Two health officers have collected the data and it is supervised by one person with a qualification of Master of public health.

Data collection procedure: The records to be reviewed were identified by their medical registration/card number. Then, together with the data clerk working at DM

follow up clinic of the hospital, data collectors had reviewed and extract data from patient charts and registries.

Data quality Assurance

The quality of data was ensured through training of data collectors and supervisor, close supervision and prompt feedback. The training consisted of instruction on extracting techniques, as per data extraction format. The data were checked for any inconsistencies, coding error, out of range, completeness, accuracy, clarity, missing values and appropriate corrections was made by the principal investigator and the supervisor consistently on the daily basis.

3.9 Data processing and analysis

3.9.1 Data processing

The data were reviewed from completed structured data retrieval form to ensure completeness and quality of data. After data quality was assured, forms were collected and assigned consecutive number (code) for ease of data entry. The Data was entered using the Epi-Info version 7.0 and clean-up has been made to check accuracy, consistency and errors identified were corrected. After the data was checked for correct entry, it was exported to STATA 14.1 software for analysis. Further data cleaning and frequency run was made to check the accuracy, consistencies missed values and variables. Cross tabulations and summary statistics were used to describe the study population in relation to relevant variables.

3.9.2 Data analysis

3.9.2.1 Descriptive statistics in Survival analysis

Let *T* be the survival time and *C* the censoring time. Define the follow-up time Y=min (T, C), and let δ denote the censoring indicator. Considering the probability density function of T, f(t) =P (T≤ t) = $\lim_{\Delta t \to 0} \frac{pr(t \leq T < t+\Delta t)}{\Delta t}$, which represents the unconditional probabilities of developing vascular complication, the survival function is defined as the complement of the cumulative distribution function, S(t)= P(T>t) giving the probability that the event has occurred after duration t and its non–increasing function. An alternative characterization of the distribution of T is the hazard function which is the instantaneous probability of

having an event at time *t* (per unit time) given that one has survived (i.e. Not had an event) up to time t and it's given as:

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t / T \geq t)}{\Delta t}$$

Estimation of Survival function

In practice, when using actual data, we usually obtain estimated survivor function and obtain curves that are step functions, rather than smooth curves.

Kaplan-meier estimator

This is a non-parametric estimator of survival function proposed by Kaplan and Meier (1958) It incorporates information from all of the observations available, both censored and uncensored, by considering any point in time as a series of steps defined by the observed survival and censored times.

Let *t1, t2,…,tn* be the survival time of *n* independent observations and *t(1)≤t(2)≤…≤t(m), m≤n* be the *m* distinct ordered vascular complication times . The Kaplan-Meier estimator of the survivorship function (or survival probability) at time t,

s(t) = p(T≥t)

$\mathbf{S_{km}(t)} = \Pi t(i) < t \left(\frac{ni - di}{ni}\right)$

Where; *t(i)* = Distinct ordered times of vascular complication

di = The number of events at time t(i)

ni = The number of individuals still at risk right before *ith* event time

The Kaplan-Meier estimator is a step function with discontinuities or jumps at the observed event times, coinciding with the empirical survival function if there is no censoring(40)

Comparisons of survival curves

In clinical research we are both concerned on estimating the survival function and, comparison of the life experience of two or more groups of Subjects differing for a given characteristic or randomly allocated to different treatments. Nowadays, the Kaplan-Meier method for estimating survival curves which plotting the corresponding estimates of the two survivor functions on the same axes of Kaplan-Meier estimator and the log-rank test for comparing two estimated survival curves are the most frequently used statistical tools in medical reports on survival data.

Log-rank test

The log rank test, developed by Mantel and Haenszel, is a non-parametric test for comparing two or more independent survival curves. Since it is a non-parametric test, no assumption about the distributional form of the data is required. The log rank test statistic for comparing two groups is given by:

$$Q_{LR} = \frac{[\sum_{i=1}^{m}(d1i - e1i)]\text{^}2}{\sum_{i=1}^{m} v1i}$$

Were; m = Rank ordered event (vascular complication) times

d1i= Observed number of event (vascular complication) in group one at event time *ti*

e1i= Expected number of event (vascular complications) corresponding to *d1i* and it is given by $\frac{n1i-di}{ni}$ were *n1i* the number of individuals at risk in group 1just prior to the event time *ti , di* the number of events (vascular complication) in both group, *ni* number of individuals at risk in both group.

v1i= variance of the number of events *di* at time *ti* and it is given by $\frac{n1inoidi(ni-di)}{ni2(ni-1)}$ were *ni and di* are the number of individuals at risk and number of (vascular complication) in both groups just prior to event time *ti* respectively.

Under the null hypothesis that two survival functions are equal, the log rank test statistic *Q* has an approximation of chi-square distribution with one degree of freedom for large samples. The null hypothesis of equality of survival functions will be rejected for large value of Q (39).

3.9.2.2 Regression models for survival data

In most medical studies which give rise to survival data, supplementary information referred to as covariates or independent variables needs to be collected on each individual, so that the relationship between survival experience of individuals and various explanatory variables have to be investigated.

Cox Proportional Hazard model

The Cox Proportional Hazard (PH) Model is a multiple regression method and is used to evaluate the effect of multiple covariates on the survival. It is semi parametric model for the hazard function that allows the addition of covariates, while keeping the baseline hazards unspecified and can take only positive values and it is defined as

$$h(t, x, \beta) = ho(t)\, e^{\beta' x}$$

were $h(t, x, \beta)$ the hazard function at time t with a covariates $X=(x_1,x_2,\ldots,x_p)'$

ho(t) the arbitrary baseline hazard function that characterizes how the hazard function changes as a function of time.

$\beta= (\beta_1, \beta_2,\ldots,\beta_p)$ is a column vector of *p* regression parameters associated with explanatory variables.

$e^{\beta' x}$ characterizes how the hazard function changes as a function of subject covariates

t is failure time

Each individual has its own hazard function of survival time. Then, the above model becomes

$h(t,xi,\beta) = ho(t)\exp(\beta_1 x_{i1}+ \beta_2 x_{i2}+\ldots+ \beta_p x_{ip})$, *I* =1,2,…,n

were n is total number of observations in the study.

Xi= (xi1 ,xi2 ,..,xip)' is a column vector of measured covariates for the *ith*

Individual (patient) which are assumed to affect the survival probability. The

assumptions of Cox proportional hazard model are:

-The baseline hazard function *ho(t)* depends on *t* , but not on covariates $x_1, x_2\ldots,x_p$

- The hazard ratio, depends on the covariates $x=(x_1,x_2,\ldots,x_p)'$ not on time.

-The covariates x_i are time independent

Parametric survival models

Parametric survival models make assumptions about the distribution of failure times and the relationship between covariates and survival experience and they fully specify the distribution of the baseline hazard/survival function according to some (defined)

probability distribution. Examples of distributions that are commonly used for survival time are: the Weibull, exponential, log-logistic, lognormal, Gompertz, and generalized gamma.

- ✓ **Exponential Distribution**

The exponential distribution is the only distribution with a constant hazard i.e $\lambda(t, \lambda) = \lambda$, $\lambda > 0$ This implies that the conditional probability of an event is constant over time. In other words, the risk of an event occurring is flat with respect to time. The survival function is $S(t, \lambda) = e^{-\lambda t}$ it can be shown that $E(T) = 1/\lambda$ and $var(T) = 1/\lambda^2$.

- ✓ **Weibull Distribution**

The Weibull model is more general and flexible than the exponential model and allows for hazard rates that are non-constant but monotonic. It is a two-parameter model (λ and ρ), where λ is the location(scale) parameter and ρ is the shape parameter ρ determines whether the hazard is increasing, decreasing, or constant over time. The shape parameter works in the following way:

- If $0 < \rho < 1$, then the hazard is monotonically decreasing with time.
- If $\rho = 1$, then the hazard is flat and we have the exponential model i.e. the Weibull model nests the exponential model. This means that we can use the Weibull model to test if the exponential model is appropriate.
- If $\rho > 1$, then the hazard is monotonically increasing with time.

- ✓ **Gompertz Distribution**

A random variable T has the Gompertz distribution with the following hazard and survivorship functions $\lambda(t, \lambda, \rho) = \lambda \exp(\rho t)$, $s(t, \lambda, \rho) = \exp(\frac{\lambda}{\rho}(1 - \exp(\rho t)))$ respectively. where the scale parameter $\lambda > 0$, and shape parameter $\rho \in (-\infty, +\infty)$.

If $\rho > 0$, then the hazard exponentially increases over time. If $\rho < 0$ then the hazard decreases exponentially over time. If $\rho = 0$then the hazard is constant and reduces to the exponential model.

3.9.2.3 Model comparison

Model comparison and selection are among the most common problems of statistical practice, with numerous procedures for choosing among a set of models(41) There are several methods of model selection. The most commonly used methods include information criteria's(AIC, BIC) and likelihood based criteria and in this case we have used these three methods to make comparison between the candidate models.

$$AIC = -2L(\Theta) + 2n_{par}$$

$$BIC = -2L(\Theta) + n_{par} \log n$$

These criteria's are used for non nested models and the model is Saied to be best model if it has the smallest AIC or BIC value (42).

3.9.2.4 Goodness of fit test

The use of diagnostic procedures for model checking diagnostics is an essential part of the modeling process.

Cox Snell residual

For all regression models, a specifically designed statistic to evaluate the accuracy of a postulated model (goodness-of-fit) is called a residual value. Residual values reflect the difference between the model-estimated values and the observed data that generated the model estimates. A simple transformation of the survival function *S*(*t*) yields Cox Snell residual values which is given by

$$r_i = -\log[So(ti)]$$

The Cox–Snell residual values have none of these properties. Their mean value and variance depend on the number of randomly censored observations, they take on only positive values, and they typically have an asymmetric distribution. When a model "fits" the data, the residual values are likely small and certainly randomly distributed When a model fails to "fit" the data in some systematic way, at least some of the residual values are likely large and nonrandom (43)

4. ETHICAL CONSIDERATION

Ethical clearance and approval to conduct the research was obtained from ethical review committee of Institute of Public, college of Medicine and Health science, University of Gondar. Since it is secondary data, it didn't require informed consent from each client rather it was informed to the head of hospital manager. Privacy of the patients were maintained, Names were not included, and questionnaires kept locked

5. RESULTS

5.1. Socio-demographic, Clinical and Physiologic Characteristics of Study Participants

In this study a total of 364 newly diagnosed type II DM patients were included but 23 (6.3%) subjects were excluded because of the missing of key variables like HDL-C, LDL-C, cholesterol and time of the start of treatment. A total of 341 patients were included in the analysis.

Majority of the study participants were females accounting 196 (57.48%) of the total sample. About 273(80.06%) of the study participants were urban dwellers. Majority of the patients 149(43.7%) included in the study was unemployed 149(43.7) followed by Government workers which was 88(25.81%) of the total sample. About 228(66.86%) of the patients had family history of DM a More than half of the patients 183(53.67%) had hypertension at the start of anti-type II DM treatment. Almost half of the type II DM patients enrolled in the study were having normal weight and 45(13.2%) were obese. About 230(67.45%) were on OHA and Majority of the patients 271(79.47%) had positive protein urea at base line.

About 234(68.62%) of the patients had HDL-C level above 40 mg/dl and more than half of the patients (54%) had LDL-C level less than 100mg/dl. More than half of type II DM patients included in the study 178(52.2%) had triglyceride level ≤150mg/dl and around 211(61.88%) of the patients were having a cholesterol level ≤200mg/dl.

Table 2: Socio-demographic, clinical and Physiologic characteristics of Type II DM patients on anti diabetic's treatment at university of Gondar referral hospital, September, 2005 – March 2017.

Variable	Frequency	Percent
Sex		
Female	196	57.48%
Male	145	42.52%
Residence		
Rural	68	19.94%
Urban	273	80.06%
Occupation		
Unemployed	149	43.7%
Government	88	25.81%
NGO	20	5.87%
Private	84	24.63%
Family history		
Yes	228	66.86%
No	113	33.14%
Hypertension		
No	158	46.33%
Yes	183	53.67%
BMI		
<18.5	29	8.5%
18.5- 24.99	169	49.56%
25- 29.99	98	28.74%
≥30	45	13.2%
Treatment		
OHA	230	67.45%
Insulin	64	18.77%
OHA + Insulin	47	13.78%
Protein urea		
Negative	271	79.47%
Positive	70	20.53%
HDL		
<40 mg/dl	107	31.38%
≥40 mg/dl	234	68.62%
LDL		
≤ 100 mg/dl	186	54.55%
>100 mg/dl	155	45.45%
Triglyceride		
≤150 mg/dl	178	52.2%
>150 mg/dl	163	47.8%
Cholesterol		
≤200 mg/dl	211	61.88%
>200 mg/dl	130	38.12%

The mean age for patents at the start of treatment was found to be 51.7(SD=11.5 years) and it ranges from 20 up to 87 years. Patients were followed for median of 81.50 months (IQR=36.07 months) and the maximum time the patient followed was 140.43 months. The median value for Creatinine 0.78(IQR=0.23 ml/s), FBS146mg/dl(IQR=77mg/dl), SBP 125mm/hg(IQR=20mm/hg) and DBP 80mm/hg(IQR 20mm/hg).

Table 3: Summary statistics of continuous variables included in the study of type II DM patients under Anti diabetic's drug at university of Gondar referral hospital, September, 2005 – March 2017.

Status of a Patient	Variable	Min	Max	Median	IQR
Censored	Time	11.20	140.43	84.15	37.58
	Age	20	87	50	50
	Creatinine	0.13	1.86	0.76	0.21
	FBS	75	347	136	48
	SBP	90	180	120	20
	DBP	60	110	80	10
Vascular complication	Time	8.07	136.20	69.80	42.10
	Age	35	82	55	55
	Creatinine	0.12	5.26	0.83	0.45
	FBS	28	460	200	97
	SBP	100	200	140	20
	DBP	65	100	90	10
Overall	Time	8.07	140.43	81.50	36.07
	Age	20	87	50	16
	Creatinine	0.12	5.26	0.78	0.23
	FBS	28	460	146	77
	SBP	90	200	125	20
	DBP	60	110	80	20

5.2. Vascular complication from type II DM

Study subjects were followed for different period of time with a median of 81.50 months (IQR=36.07 months) the minimum time the patient was followed is 8.06 months and the maximum time was 140.43 months after the start of treatment. Based on this the total person time observation was found to be 28692.8 person months. During the follow up period a total of 97(28%) newly diagnosed patients who were free from any complication at the start of their treatment have developed at least one of the vascular complications.

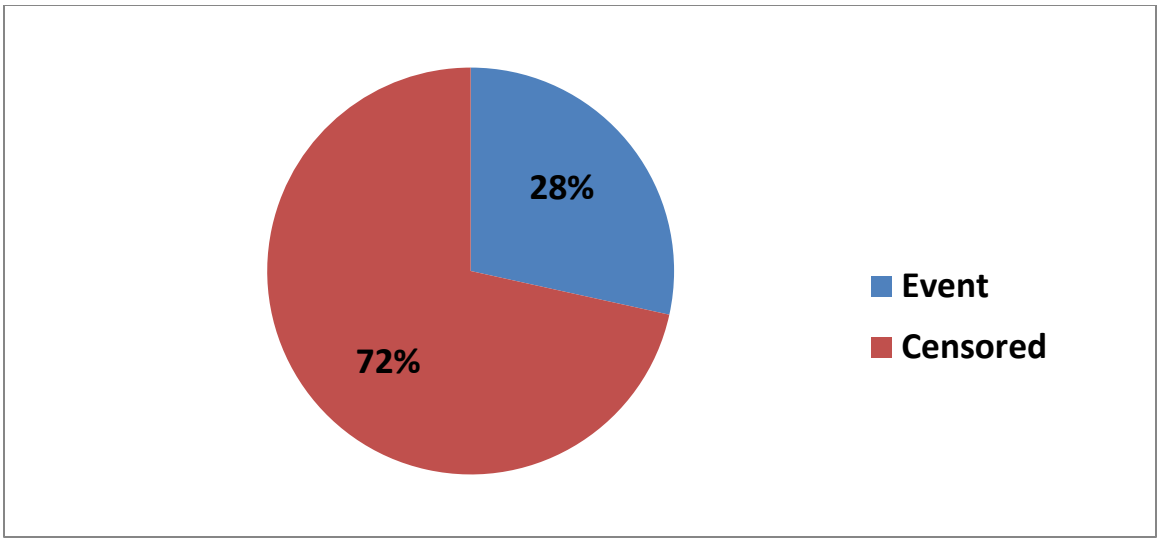

Figure 2: Pie chart showing the proportion of event and censored patients among type II DM patients in university of Gondar referral hospital from September 2005 March 2017.

Out of a total of vascular complications the largest proportion 38(38.54%) was found to be neuropathy followed by nephropathy 26(27.8%), stork 8(8.83%) retinopathy 7(7.29%) and equal number of subjects 9(9.38%) have developed CHD and PAD.

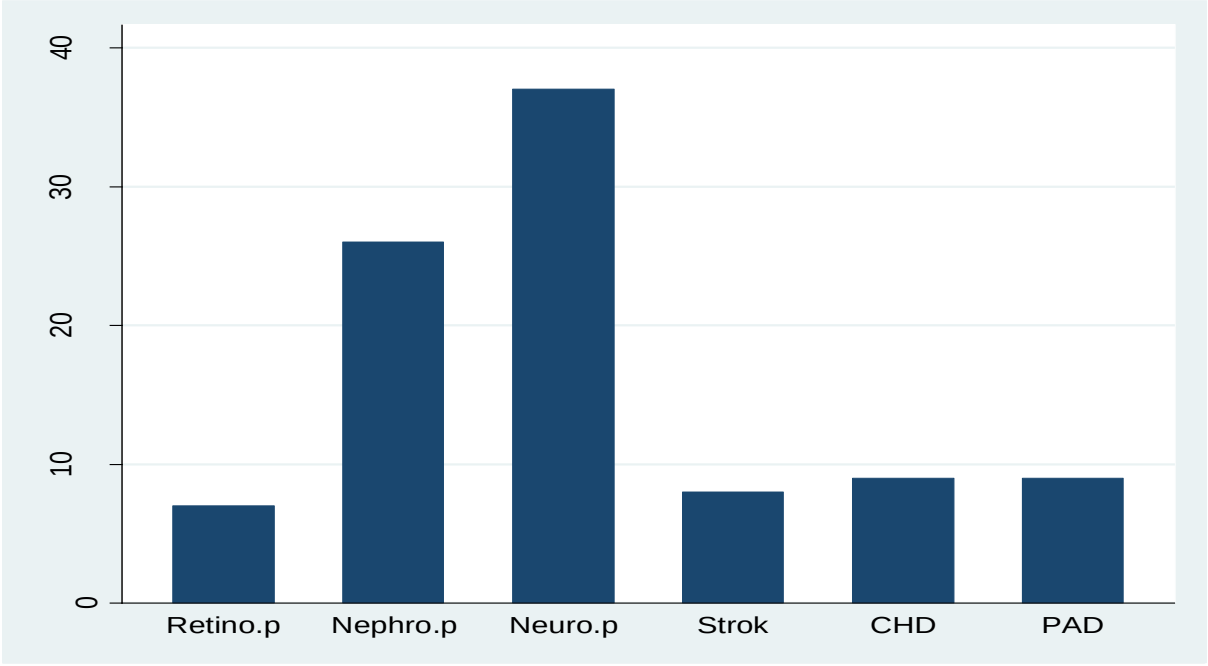

Figure 3: Frequency distribution of the type of vascular complications among type II DM patients on anti-diabetics treatment at university of Gondar referral hospital, September, 2005 – March 2017.

The incidence of vascular complications was found to be 40.6 cases (95% CI:,33.2, 49.5) per 1000 person year observation and from this the incidence of retinopathy was 18.4 (95% CI: 8.8, 38.6), nephropathy 14.4(95% CI: 9.8, 21.4), neuropathy 18.9(95%CI: 13.7, 25.9), stork 17.0(95%CI: 8.5, 33.9), CHD 16.7(95%CI: 8.7, 32.1) and PAD 15.1(95%CI: 7.9, 29.0) cases per 100 person year observation.

The cumulative probability of developing vascular complication among Type II DM patients who were free from any of the complications at the start of the treatment was 0.0423 at month 40, 0.1653 at month 70, 0.3726 at month 100, 0.5587 at month 120 and 0.8617 at month 140 during the follow up time. The median survival time was found to be 110.5 months (fig 4).

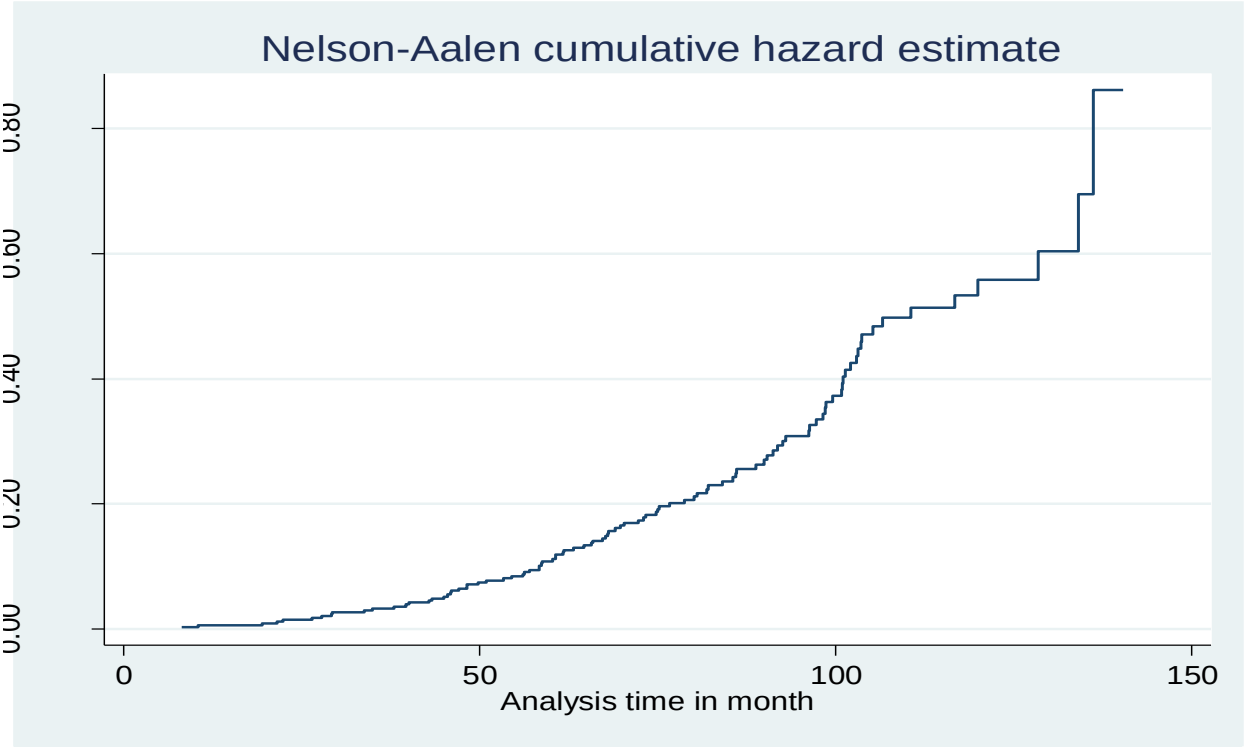

Figure 4: The Nelson-Aalen estimated cumulative curve showing cumulative probability of vascular complication among type II DM patients on anti diabetic's treatment at university of Gondar referral hospital, September, 2005 – March 2017.

5.3. Predictors of vascular complication among type II DM patients

A separate graph of estimates of Kaplan meier survival functions had been constructed for different categorical variables. By doing this it was possible to see the existence of difference in survival experience between individuals of the indicated categories. In

general the pattern of the survivorship function lying above another means the group defined by the upper curve has a better survival than the group defined by the lower curve. The Kaplan mere survival function plot for all categorical variables was done(Appendix 4, fig A-L) From this type II DM patients who had hypertension at baseline have less survival than patients who had no hypertension (fig 5).

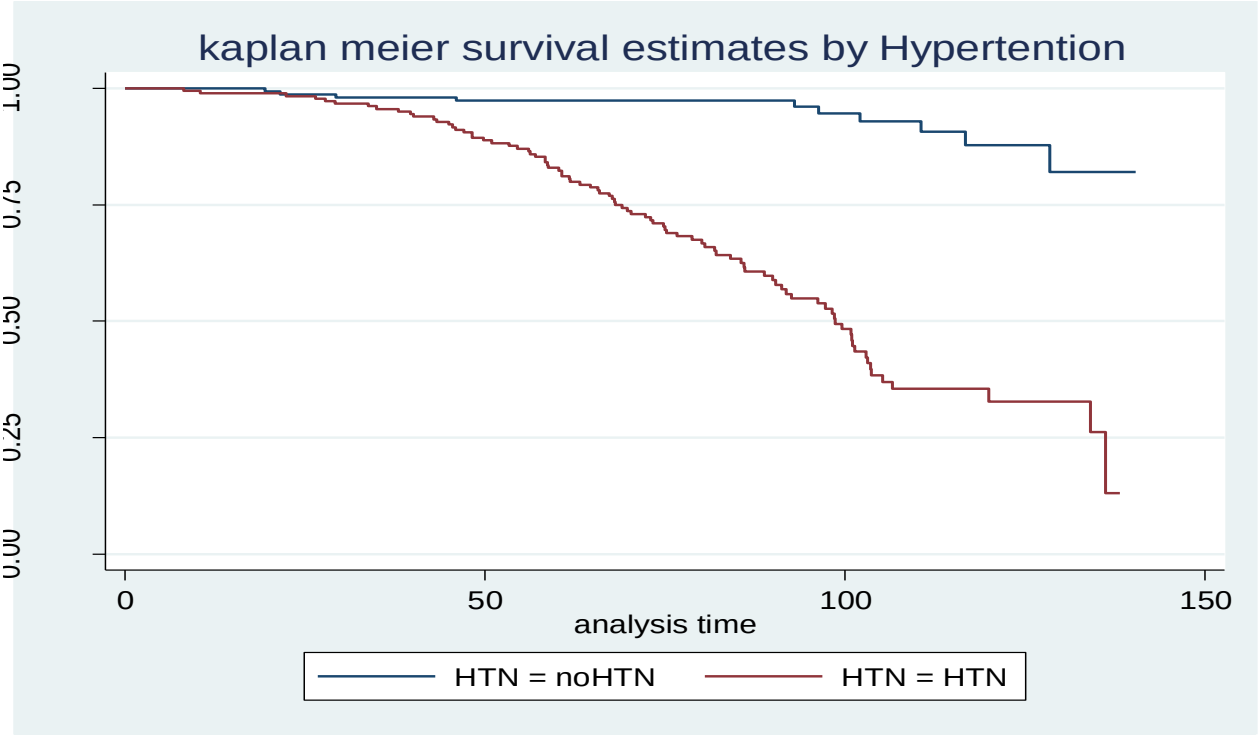

Figure 5: Kaplan Meir survival curve showing hazard of vascular complication by hypertension status at baseline among type II DM patients on anti diabetic's treatment in university of Gondar referral hospital, September, 2005 – March 2017.

The log rank statistical method was used to check whether there is a significant difference in the survival functions among categories that is shown using Kaplan meier estimates of survival functions. Based on the result of log rank test there were a significant difference in survival among categories of sex, occupation, protein urea, HTN, HDL-C, LDL-C, triglyceride, cholesterol and BMI. However there is no significant difference among categories of residence and treatment type.

Type II DM patients who have no history of hypertension at the start of diabetes treatment had longer survival experience than Type II DM patients with history of hypertension which is supported by log rank test(log rank $Chi^2(1)=72.7$, p-value=0.000)

Type II DM patients with Negative protein urea at the start of diabetes treatment has a better survival experience than that of type II DM patients with positive protein urea which is supported by log rank test (log rank $Chi^2(1)= 52.91$, p-value=0.0000

Table 4: Results of the Log-rank test for the categorical variables of type II DM patients on anti diabetic's treatment in university of Gondar referral hospital, September, 2005 – March 2017.

covariate	df	Chi-square	P-value
Sex	1	12.01	0.0005
Residence	1	1.76	0.1851
Occupation	3	15.85	0.0012
Protein urea	1	52.91	0.0000
Treatment	2	0.72	0.6964
HTN	1	72.7	0.0000
HDL	1	113.9	0.0000
LDL	1	106.08	0.0000
Triglyceride	1	66.86	0.0000
Cholesterol	1	54.51	0.0000
BMI	3	32.33	0.0000

Assessing the proportional hazard assumption

In order to fit a model we have to asses some requirements of the model that means the model should be assessed whether it describe our data well or not. In this case the main aim is testing the proportional hazard assumption and measuring the overall goodness of fit of the model. The proportional hazard assumption states that the risk of failure of the study subjects must be the same no matter how long they are followed.

The plot of log [- log (survival probability) versus log of survival time was done for different categories of predictor variables (Appendix 6, fig A-G). As it is observed from the plot of two categories of sex and LDL-C the two lines were nearly parallel which means that the proportional hazard assumption was valid.(fig 6)

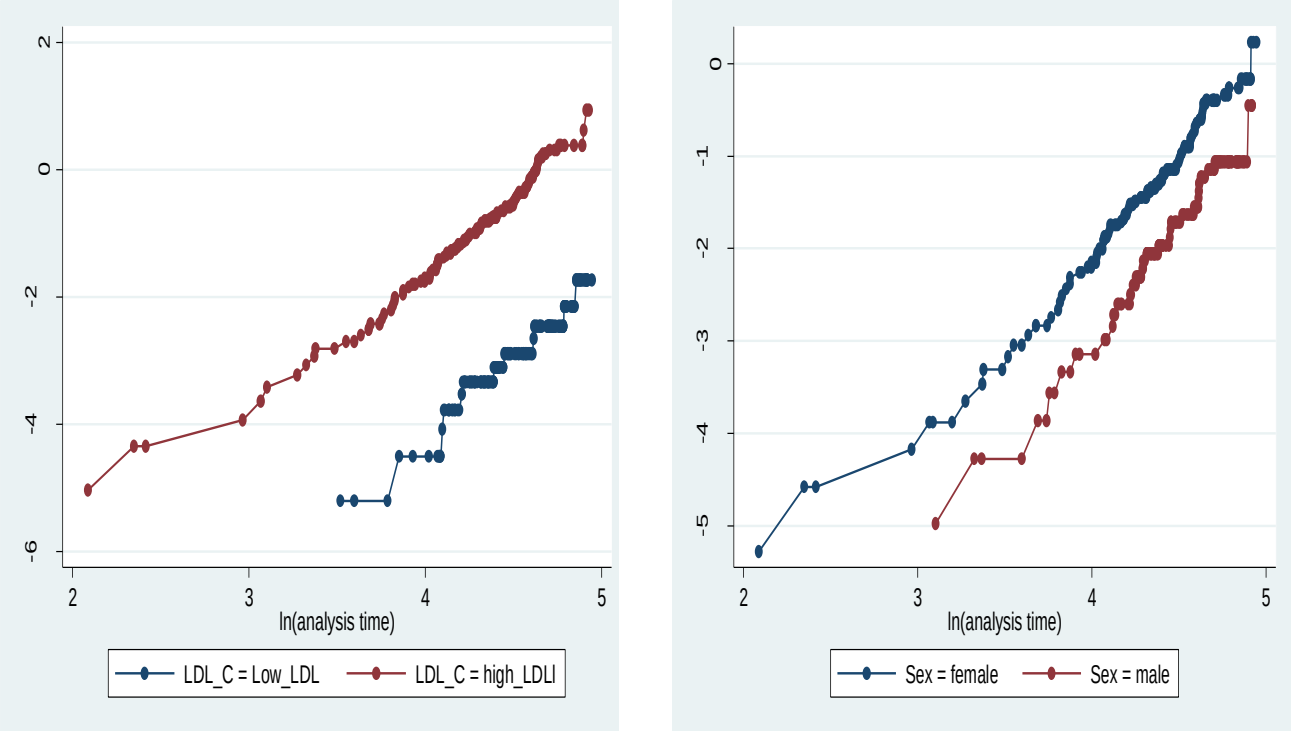

Figure 6: Plot of log (-log(survival probability)) Vs log (survival time) by LDL-C and sex for type II DM patients on ant diabetics treatment at university of Gondar referral hospital September,2005-March 2017.

The interaction of each of the covariates with time was also assessed and all of time dependent interactions was not significant (Appendix 3, Table 1).

The global test of proportional-hazards assumption based on the Schoenfold residuals was also done and It was found that all of the covariates and full model satisfies the proportional hazard assumption (Chi square= 16.37, p-value= 0.5102) (Appendix 3, Table 2)

In the process of model development, it is relevant to check whether the correct functional form of a continuous covariate that is/are included in the multivariable model was used. Based on this the assumption of linearity is fulfilled for Age, Creatinine, Fasting blood sugar, Diastolic blood pressure, and Systolic blood pressure.

Model comparison

After proportional hazard assumption was checked both semi-parametric and parametric proportional hazard models were fitted to estimate the survival time to develop vascular complications and identify predictors among type II DM patients. the most parsimonious mode were chosen by using information criteria's(AIC, BIC) and Log likelihood.

Based on all the three comparison techniques used the Gompertz regression model(AIC=277.7724, BIC=369.7376, log likelihood=-114.8862) was found to be more efficient than Cox-PH and other parametric models. Following this all two and three way interaction terms were checked to assess their importance in predicting time to vascular complication. However, none of them had significant contribution. Interpretations and conclusions were thus be based on Gompertz model.

Table 5: Summary of Model comparison between semi-Cox proportional hazard models and parametric Cox- Regression models using AIC, BIC and log likelihood

Comparison methods	**Models**			
	Cox PH model	*Exponential*	*Weibull*	*Gompertz*
Log likelihood	-408.4529	-167.57514	-115.9195	-114.8862
AIC	860.9258	381.1515	279.8319	277.7724
BIC	945.2272	469.2848	371.7971	369.7376

After fitting a univareate Gompertz proportional hazard model all the predictor variables were found to have p-value <0.2 after this a multivariable model were fitted and covariates like Sex, Hypertension status at baseline, protein urea at baseline, HDL-C level, LDL-C, Triglyceride level were found to be significant predictors for time to develop vascular complication among type II DM patients at 5% level of significance.

The hazard of developing vascular complication is decreased by **50%** among male type II DM patients than female type II DM patients keeping other variables constant**. (AHR= 0.50, 95%: 0.27, 0.94)**

The hazard of developing vascular complication is increased by **69%** among type II DM patients with positive protein urea than patients with negative protein urea keeping other variables constant. **(AHR= 1.69, 95%CI: 1.03, 2.78)**

The hazard of developing vascular complication for patients with type II DM who have hypertension at baseline is **3.99** times the hazard of patients who have no hypertension at baseline keeping other variables constant**.(AHR= 3.99, 95%CI: 1.87, 8.56)**

The hazard of developing vascular complication is decreased by **57%** among type II DM patients with high HDL level (≥ 40 mg/dl) than patients with low HDL-C level (<40mg/dl) keeping other variables constant**.(AHR= 0.43, 95%CI: 0.24, 0.77)**

The hazard of developing vascular complication type II DM patients with high LDL-C level (>100 mg/dl) is **3.05** times the hazard of patients with low LDL level (≤100 mg/dl) keeping other variables constant**.(AHR= 3.05, 95%CI: 1.47, 6.35)**

The hazard of developing vascular complication among type II DM patients with high triglyceride level (>150mg/dl) is **2.74** times the hazard of patients with low triglyceride level (≤150mg/dl). **(AHR= 2.74, 95%CI: 1.28, 5.84)**

Table 6: Multivariable analysis using the Gompertz Cox-Regression model for predictor's vascular complication among type II DM patients in university of Gondar referral hospital September, 2005 – March 2017.

Variable	Survival Status		Crud HR (95% CI)	Adjusted HR (95% CI)
	Event	Censored		
Age			1.04(1.03, 1.06)	1.02 (0.99, 1.04)
Sex				
Female	68	128	1	1
Male	29	116	0.47(0.31, 0.73)	0.50(0.27, 0.94)*
Residence				
Rural	14	54	1	1
Urban	83	190	1.47(0.84, 2.60)	0.51(0.25, 1.02)
Occupation				
Unemployed	57	92	1	1
Government	17	71	0.80(0.41,1.57)	0.796(0.41, 1.56)
NGO	4	16	0.38(0.14,1.05)	0.85 (0.27, 2.70)
Private	19	65	0.52(0.31,0.88)	0.83 (0.39, 1.74)
Family history				
Yes	50	178	1	1
NO	47	66	2.17(1.45, 3.23)	1.25 (0.78, 2.01)
Treatment Type				
OHA	67	163	1	1
Insulin	16	48	0.79(0.45, 1.36)	0.50(0.28, 1.01)
Insulin + OHA	14	33	0.87(0.46, 1.67)	0.91(0.48, 1.72)
BMI				
18.5 – 24.99	32	137	1	1
<18.5	5	24	0.82(0.32, 2.10)	1.07(0.34, 3.27)
25-29.9	36	62	2.04(1.27, 3.29)	0.66(0.37, 1.16)
≥30	24	21	4.22(2.47, 7.21)	0.84(0.44, 1.61)
HTN status				
No HTN	10	148	1	1
HTN	87	96	10.57(5.48, 20.38)	3.99(1.87, 8.56)***
SBP			1.03(1.0, 1.04)	0.995(0.97, 1.01)
DBP			1.07(1.05, 1.09)	1.02(0.99, 1.05)
HDL-C				
<40mg/dl	71	36	1	1
≥40mg/dl	26	208	0.12(0.07, 0.18)	0.43(0.24, 0.77)**
LDL-C				
≤100mg/dl	12	174	1	1
>100mg/dl	85	70	13.12(7.14,24.10)	3.05(1.47, 6.35)**

Cholesterol level				
≤200mg/dl	27	184	1	1
>200mg/dl	70	60	4.67(2.99, 7.28)	0.76(0.43, 1.36)
Triglyceride				
≤150mg/dl	13	165	1	1
>150mg/dl	84	79	8.08(4.50, 14.49)	2.74(1.28, 5.84)**
FBS			1.008(1.006,1.010)	1.00(0.999,1.005)
Creatinine			1.003(0.995,1.010)	100(0.995, 1.009)
Protein urea				
Negative	54	217	1	1
Positive	43	27	4.14(2.77, 6.19)	1.69(1.03, 2.78)*

LR test $chi^2(22)$ = 202.07 *Prob > chi2 = 0.0000*

*** p-value<0.001* **p-value<0.01* *p-value<0.05*

The shape parameter gamma was found to be 0.37 (95% CI:0.29, 0.44) which is positive. This indicates that the hazard of vascular complications increases exponentially with time.

Goodness of fit test

The Cox- Snell residuals (together with their Nelson-Aalen cumulative hazard function) had been obtained from fitting using the exponential, Weibull, Gompertz models to our data (Appendix 5). It can be seen that the plot of the Nelson Aalen cumulative hazard function against Cox-Snell residuals is closest to 45^0 straight line through the origin for Gompertz model when compared to Weibull and Exponential. This suggests that the Gompertz model provided the best fit for our data set (fig 6).

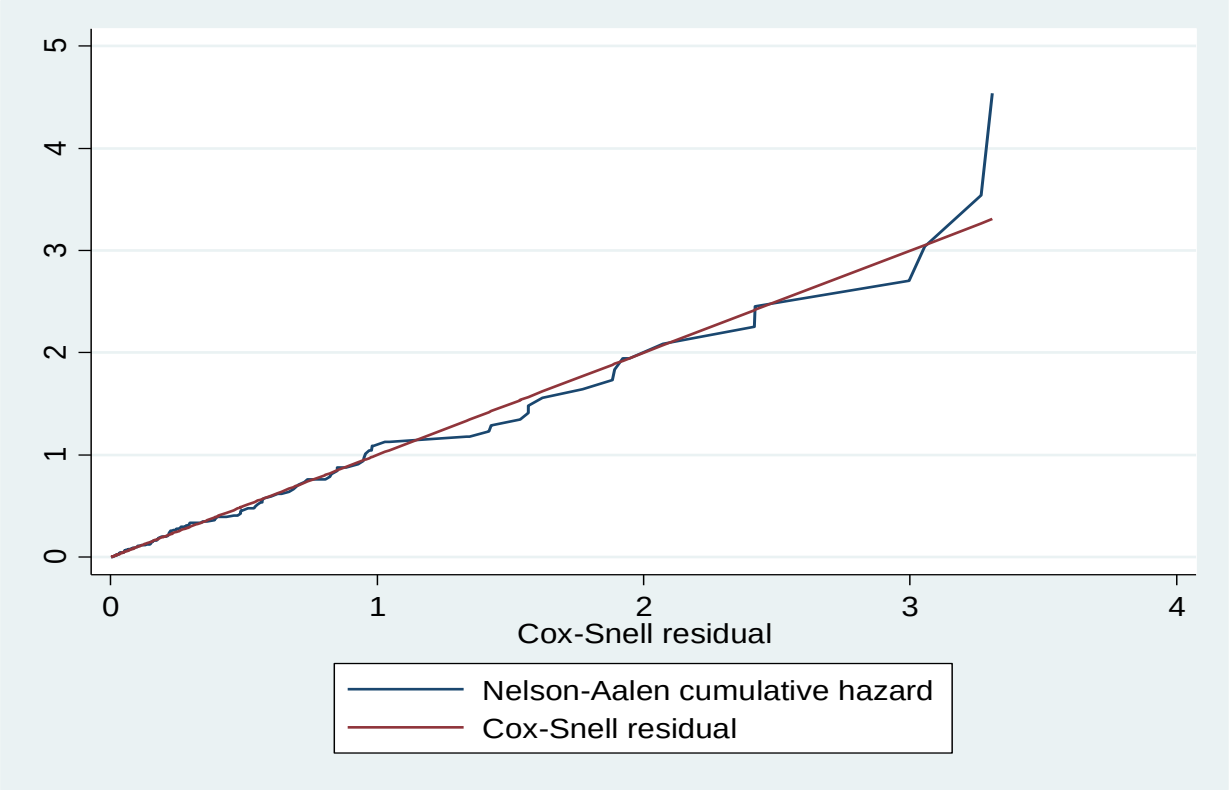

Figure 7: Cox-Snell residual obtained by fitting Gompertz model for type II DM patients under ant diabetic's treatment in University of Gondar Referral hospital September, 2005 –March 2017.

6. DISCUSSION

This study mainly investigated the incidence and determinates of vascular complication among type II DM patients in university of Gondar referral hospital, Ethiopia. Many other studies reported different risk factors for vascular complication; our study also assessed socio-demographic, clinical and physiologic characteristics of the patients based on the records from their medical follow up chart. As a result factors like male sex, having hypertension at baseline, positive protein urea, HDL-C level ≥40mg/dl, LDL-C level >100mg/dl and Triglyceride >150mg/dl were found to be significantly associated with vascular complication.

During the study period the cumulative incidence of vascular complications after a median follow up time of 6.8 years were 28%. This result was a little bit lower than the study done in Taiwan (23) which showed the Incidence to be 30.7% after a median follow up time of five years. In this we found the incidence rate to be 40.6 cases per 1000 person year observation. The incidence of CHD and Stroke was found to be 16.7 and 17.0 cases per 100 person year observation in our study; this was also lower than a study in India(44) which showed the incidence rates to be 216 and 115 cases per 1000 person year observation respectively. The incidence rate of retinopathy was 18.4 cases per 100 person year observation was also lower than other study done in Kenya(45) which showed the incidence to be 224.7 cases per 1000 person year observation. This could be due to the difference in median follow-up time (India=13 years), age of the study participants because the study in Kenya used patients above the age of 50 and the difference could also be due to the difference in diagnostic methods used By the studies. In contrast to this the incidence of retinopathy (18.4) nephropathy(14.4) neuropathy(18.9) and PAD(15.1) cases per 100 person year observation were found to be higher than other study in India(46) which showed the incidence of retinopathy, nephropathy, neuropathy and PAD to be 78, 58, 13.9, 2, 5.4 cases per 1000 person year observation. This could be due to and short follow up time(5.7 years) used by the Indian study.

In our study male type II DM patients accounted only 29.9% of the events and they were found to have lower risk of developing vascular complication than female patients. This

is in line with three studies done in Ethiopia (18), India(47) and met analysis (7) which showed female patients to have higher risk to develop vascular complications. This could be due to the hormonal differences because female patients encounter hormonal imbalance or decreased estrogen level at menopause and at the same time they lose the vasodilatory and anti-inflammatory activity of estrogen and this will lead to endothelial dysfunction(48). Other reason could be due to sex specific factors like polycystic ovarian syndrome, preeclampsia and gestational DM(49).Other possible reason could be high exposure of males for physical activities. Because Physical activity contributes to improve insulin sensitivity and to decrease blood glucose level and weight loss(50). In contrast to our result other retrospective follow up studies done in Iran(15) and Japan(16) showed males to be at increased risk of developing vascular complications. Therefore there is a need of further research to determine if this sex difference contributes to the better outcomes in man with diabetes.

In our study it was found that type II DM patients who had hypertension at base line had an increased risk of developing vascular complications. This result is consistent with other studies done in Iran(15), Japan(16), India(26), and Ireland(28) which showed having hypertensions puts the patients at higher risk for both macro and micro vascular complications. Some other studies In Cameroon and morocco investigated the association between hypertension and specific complications; in this regard Type II DM patients with hypertension were at increased risk of nephropathy and cardio vascular events (29, 30). The possible reason could be the hypertension can affect endothelial cell structure and functioning that leads to enhanced growth and vasoconstriction; this changes to the endothelium has a key role in the development of arthrosclerosis and glomerulosclerosis this finally predispose patients for vascular complications(51).

In this study increased Triglyceride level>150mg/dl and LDL-C level>100mg/dl were found to increase the risk of vascular complication but HDL level ≥ 40mg/dl was associated with decreased risk of vascular complications. This result was in accordance with other studies done in India (21),Singapore (37), Zimbabwe (32) and multi-centered study involving 28 countries from Asia Africa Europe and south America (36). These four studies showed that patients with higher levels of LDL- cholesterol to

have higher risk to develop vascular complication but patients with the higher levels of HDL-cholesterol have decreased risk. Our result was also consistent with Other study in India which showed increased level of triglycerides to increase the risk of developing vascular complications like stroke and CHD(44). This could be due to their function. Since the function of HDL cholesterol is transport of fats (lipids) Away from the artery wall to the liver this eventually reduces risk of accumulation fats and arthroscleroses within the arterial wall and at the same time it protects the inner wall of the arteries from damage so this reduces the risk of CHD, Stork and other vascular diseases (52). The reverse is true for LDL cholesterol because LDL -C transports fates (lipids) to the arteries which in turn produce arthrosclerosis in the arteries so this increases the risk of vascular complication(53). Excess level triglycerides above the normal range (>150mg/dl) also produces plaque in the arteries so it increases the risk of vascular complications. In our study it was found that patients with positive protein urea have an increased risk of having vascular complication this may be due that protein urea is an early sign to the damage for kidneys so patients with positive protein urea are at increased risk of vascular complications like nephropathy in the long run(54).

The clinical importance of this study was to provide information for health professionals and patients about factors that are associated with the risk of vascular complication and to act on them to minimize the risk and maximize their effort on prevention of having the problem and the public health importance of this study is the to prevent economic loss associated with the diseases and its complications.

7. STRENGTH AND LIMITATION

Strength of the study

- Patents were followed for long duration with a maximum of 11 and half years
- Implementation of parametric estimation was also the strength of this study

Limitation of the study

- As this study was conducted based on secondary data, data on some potentially Important predictors were not available.
- This study was only done among patients who had follow up in university of Gondar hospital so it is better to include wide area.
- The study assumed all the vascular complications are caused by diabetes mellitus.

8. CONCLUSION

In this retrospective follow up study we found that the rate of vascular complication among type II DM patients in university of Gondar referral hospital was relatively low.

Hypertension at baseline, LDL-C>100mg/dl, triglyceride >150mg/dl, HDL-C≥40 mg/dl and male sex was significant predictors of vascular complication.

9. RECOMMENDATIONS

To health professionals:

-Health professionals should give greater attention to patients with deslipedemia, protein urea and hypertension co morbidity together with that of DM

To the patients

-Diabetes mellitus patients with hypertension co-morbidity should strictly control the hypertension like that of the diabetes

To researchers

-Although this research is very useful in understanding vascular complications; there is a need of further research on different areas of the countries, by including nutritional history, and behavioral factors like level of physical activity, smoking and alcohol consumption history.

-It’s better to us prospective study

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11. APPENDICES

Appendix 1: **- Information Sheet**

Title of the Research Project: Incidence and risk factors for vascular complication among type II DM patients in university of Gondar referral hospital. A retrospective follow-up study

Name of Principal Investigator: Haileab Fekadu

Name of the Organization: University of Gondar, College Of Medicine and Health Sciences, Institute of Public Health

Sponsor: University of Gondar

Purpose of the Research Project: The main purpose of this research project is to measure vascular complication and its risk factors among Type II DM patients in university of Gondar referral hospital.

Introduction: This information sheet is prepared for University of Gondar referral hospital Hospital's administration and hospitals chronic diseases follow up coordinating office. The aim of the form is to make the above concerned offices clear about the purpose of research work, data collection procedures and get permission to undertake the research.

Procedure: In order to achieve the above objectives, cards of selected type II DM patients who are newly diagnosed between September 2005 and august 2012 will be included

Risk and /or Discomfort: By participating in this research project, there is totally no risk that comes to one whom document is reviewed where as the review is of great importance to the research project; which is in turn important for overall planning of the program.

Benefits: The research have no direct benefit for one whose document/record is included in this research. But the indirect benefit of the research for the participant and all other clients in the program is clear. This is because if program planners are preparing predicted plan there is a benefit for clients in the program of getting appropriate care and treatment services. Of all, the research work has a paramount direct benefit for health care planners and managers, especially for those on chronic diseases program planning and management

Confidentiality: To keep the confidentiality of the records of the clients, the record will be extracted by healthcare professionals. Then data collectors will review the selected charts. The information collected from this research project will be kept strictly confidential and information reviewed about the clients by this study will be stored in a file, without name i.e. investigator uses number codes to the record during the review. The information gathered will not be accessible to anyone except the principal investigator and will be kept locked with password and appropriate locks.

Person to contact: This research project will be reviewed and approved by the Institutional Review Board of College of Medicine and Health Sciences, University of Gondar. If in case you want to know more information about the research and its undertakings, you can contact the committee through the address of the advisor and/or the principal investigator below.

1. **Dr. Asrat Atsedeweyen (PhD),** University of Gondar, College of Medicine and Health Sciences, Institute of Public Health, Department of Epidemiology and Biostatistics: Advisor Tel: +251-930001197
2. **Mr. Adissu Jember (Msc**): Gondar University, College of Medicine and Health Sciences, Institute of Public Health, Department of Epidemiology and Biostatistics: Advisor Tel: +251-945014569
3. **Haileab Fekadu**: University of Gondar, College of Medicine and Health Sciences, Institute of Public Health, Department of Epidemiology and Biostatistics: principal investigator

Tel: +251-918-255964 e-mail: haileabfekadu@gmail.com

Permission: Lastly but not least, you are kindly requested to permit and forward your Permission to concerned body in your organization so that the researchers can get Cooperation from the data clerks and other responsible bodies in place.

Appendix 2: Data collection Check list

This checklist is prepared for the collection of socio-demographic, clinical, treatment and outcome related information that are important for the assessment of outcome and predictors of vascular complication of DM in University of Gondar Hospital. All this information will be retrieved from individual patient card without mentioning the name of clients. This information will be collected by health care providers (BSc nurse or Health Officer) possibly working in chronic diseases follow up clinic. **Contact Information** ***Haileab Fekadu +251918255964***

S.No	Variables	Categories
01	Patient MRN number	
02	Age	_____**yer**
03	Gender	0. Female 1. Male
04	Residence	0. Rural 2. Urban
05	Occupation	0.Unemployed 1.Government 2.Nongovernment 3. Private
06	Family history of DM	0.yes 1.No
07	Date of diagnosis	_____/_____/_____
08	FBG level	_____ Mg/dl
09	Weight	_____Kg Ht_____mt
10	Treatment start date	_____/_____/_____
11	Type of treatment	0. OHA 1. Insulin 2. OHA and insulin
12	Duration of diabetes	_____yer
13	R. SBP	_____mm/hg
14	R. DBP	_____mm/hg
15	Protein urea	0. Negative 1. Positive
16	Creatinine level	_____ __ml/s
17	HDL -C	_____mg/dl
18	LDL-C	_____mg/dl
19.	T. cholesterol	_____mg/dl
20	Triglyceride	_____mg/dl
21	Hypertension	1. Yes 2. No

22	Vascular complication	1. Retinopathy ---------/---------/-------- 2. Nephropathy --------/-------/------- 3. Neuropathy------/-----/---- 4 . Stroke -------/--------/----- ---- 5. CHD ------/-----/---- 6. PAD ------/-----/---- 7. No
23	Diagnosis time for the first event	---------/--------/----------
24	Last status of patient	1. Lost follow-up---------/-------/-------- 2. Died --------/---------/--------- 2. Alive 4. Transferred out 5. Other

Baseline measurements

Date (D/M/Y)	FBS	SBP	DBP	Protein urea	Complication	Creatinine	Treatment

Collected by: Name _____ Signature _____Date _____

Supervised by: Name _____ Signature _____ Date _____

Appendix- 3

Table1: Interactions of each of the covariates with time among type II DM patients in university of Gondar referral hospital September, 2005 to August, 2012.

Variables	Hazard ratio	Std. err	P-value	95% CI
*Age*t*	1.000296	0.0003177	0.351	0.999674, 1.000919
*Sex*t*	1.003787	0.0081563	0.642	0.9879272, 1.019901
*Residence*t*	1.009742	0.0106959	0.360	0.988945, 1.030924
*Occupation*t*	1.001665	0.0034266	0.627	0.994971, 1.008403
*Family history*t*	1.009614	0.0074468	0.195	0.9951231, 1.024315
*Protein urea*t*	1.012375	0.007577	0.100	0.997633, 1.027335
*Treatment type*t*	1.001776	0.005004	0.722	0.9920162, 1.011632
*Creatinine*t*	1.004912	0.0044586	0.269	0.962113, 1.013689
*HTN*t*	1.000375	0.0118728	0.975	0.977373, 1.023918
*HDL*t*	0.9864459	0.0080768	0.096	0.970742, 1.002404
*LDL*t*	0.9970929	0.0110624	0.793	0.9756452, 1.019012
*Triglyceride*t*	1.015449	0.0110133	0.157	0.9940911, 1.037266
*Cholesterol*t*	1.015074	0.0084022	0.071	0.9987383, 1.031676
*BMI*t*	1.001824	0.0046514	0.695	0.9927487, 1.010982
*FBS*t*	1.000095	0.00004466	0.342	0.99922, 1.0009708
*SBP*t*	0.9999026	0.0001784	0.585	0.9995531, 1.000252
*DBP*t*	0.9999532	0.0003738	0.900	0.9992208, 1.000686

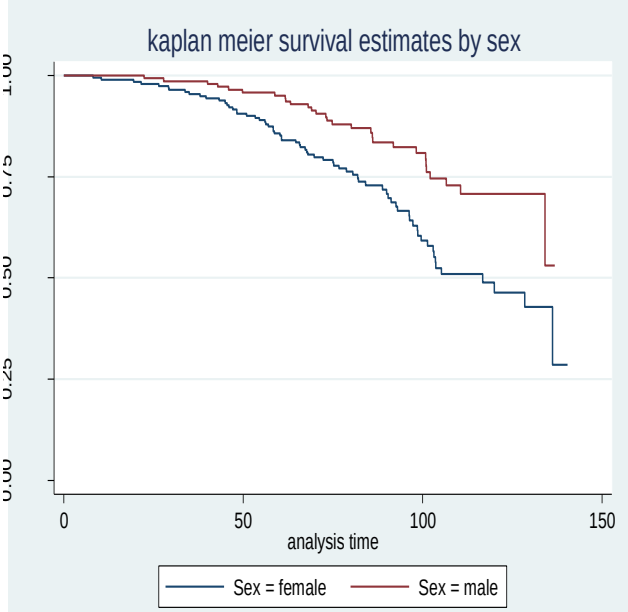
Table2: test of proportional hazard assumption based on schoenfold residuals for the covariates among type II DM patients in university of Gondar referral hospital September 2005 to August 2012.

Variable	rho	Chi-square	df	P-value
Age	0.05130	0.29	1	0.5882
Sex	-0.01568	0.02	1	0.8831
Residence	-0.00413	0.00	1	0.9625
Occupation	0.03662	0.14	1	0.7070
Family history	0.11395	1.55	1	0.2132
Protein urea	-0.03467	0.17	1	0.6828
Treatment type	-0.02113	0.05	1	0.8253
Creatinine	0.02624	0.07	1	0.7937
HTN	0.05382	0.35	1	0.5518
HDL-C	-0.16743	1.92	1	0.2265
LDL-C	-0.14251	2.38	1	0.1228
Triglyceride	0.05208	0.41	1	0.5214
Cholesterol	0.12571	2.06	1	0.1512
BMI	-0.05820	0.38	1	0.5398
FBS	0.08971	0.93	1	0.3343
SBP	-0.04533	0.17	1	0.6826
DBP	-0.15322	2.44	1	0.1185
Global test		16.37	17	0.5102

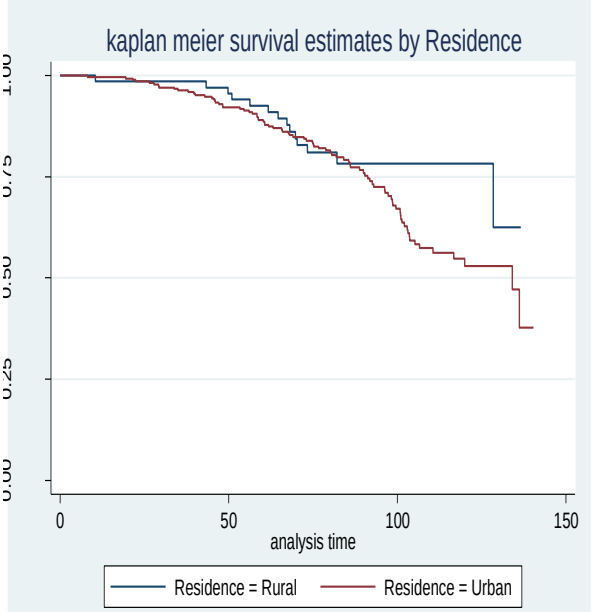
Appendix 4

Figure: Plots of Kaplan-Meier survivor functions based on different factors, of type II DM patients under ant diabetic's treatment in university of Gondar referral hospital September, 2005 – August, 2012.

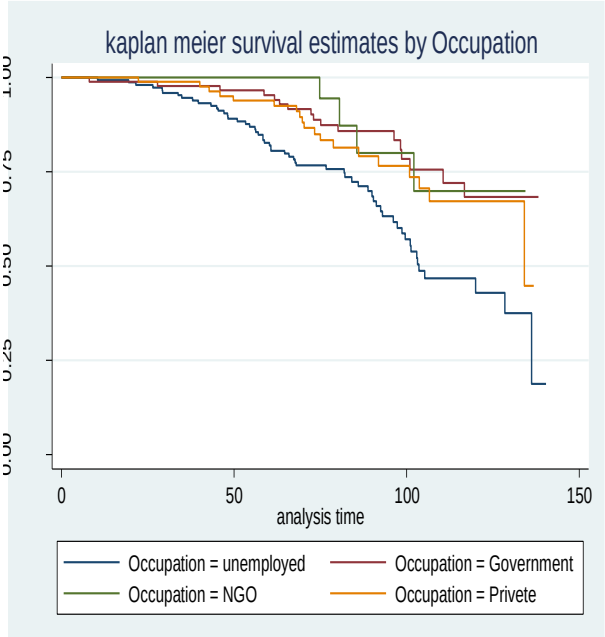
A



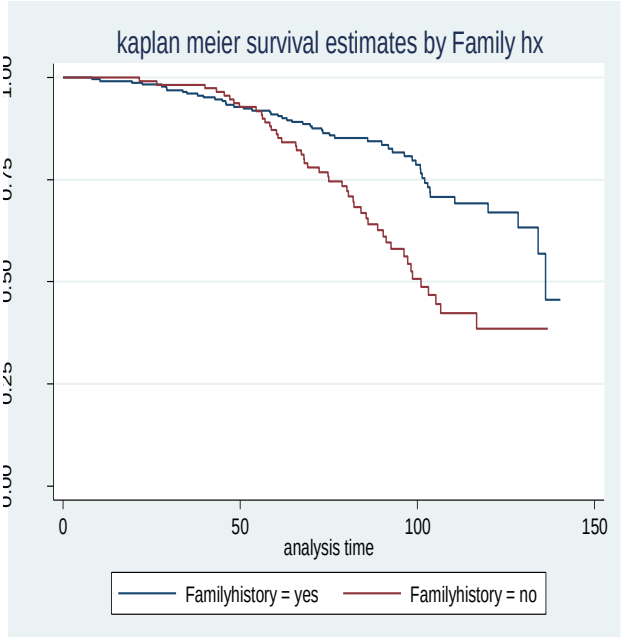
B



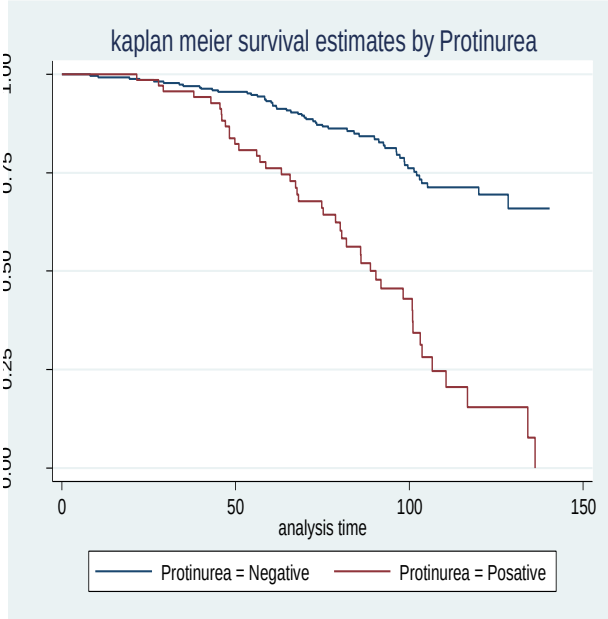
C.



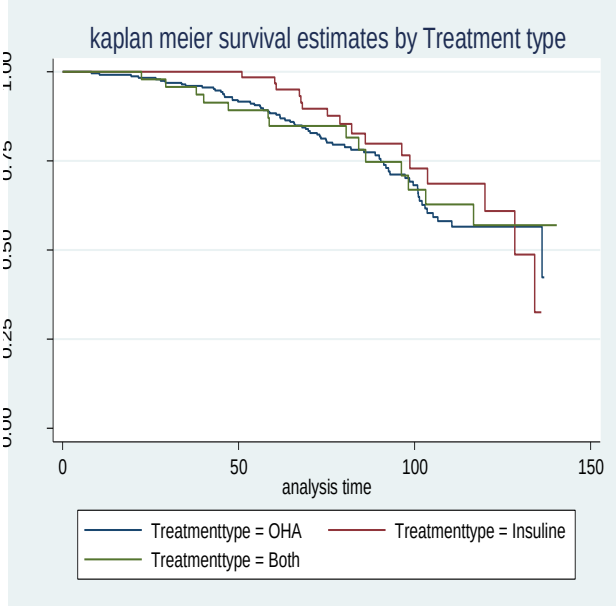
D.



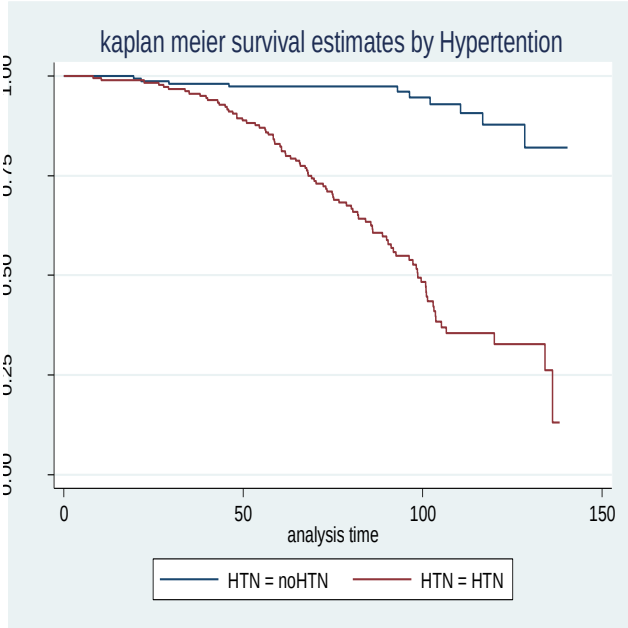
E.


kaplan meier survival estimates by Protinurea
0.00
0.25
0.50
0.75
1.00
0
50
100
150
analysis time
Protinurea = Negative
Protinurea = Posative

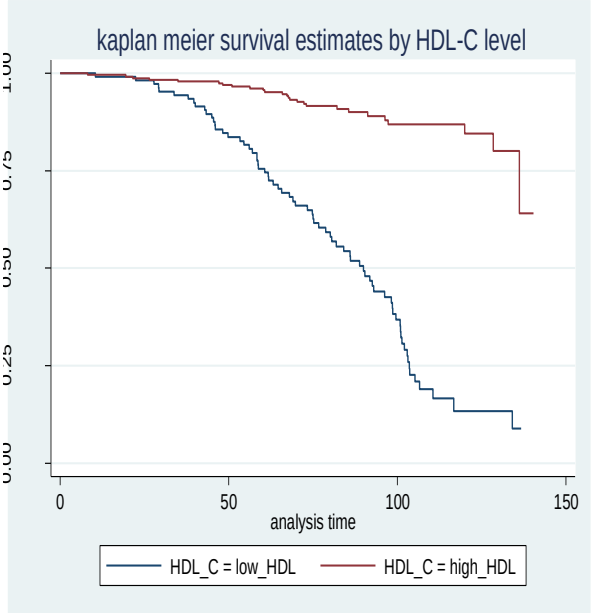
F.


kaplan meier survival estimates by Treatment type
0.00
0.25
0.50
0.75
1.00
0
50
100
150
analysis time
Treatmenttype = OHA
Treatmenttype = Insuline
Treatmenttype = Both

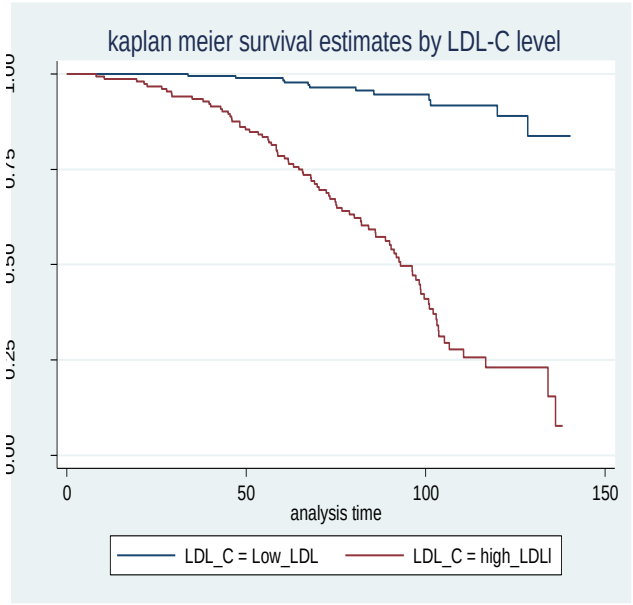
G.


kaplan meier survival estimates by Hypertention
0.00
0.25
0.50
0.75
1.00
0
50
100
150
analysis time
HTN = noHTN
HTN = HTN

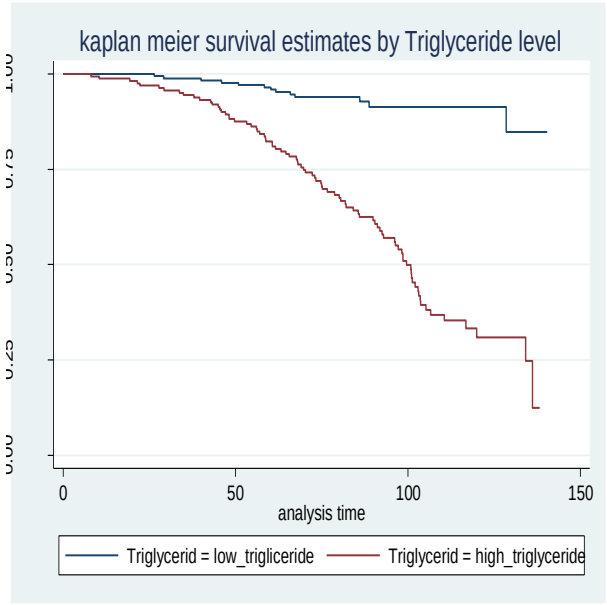
H.


kaplan meier survival estimates by HDL-C level
0.00
0.25
0.50
0.75
1.00
0
50
100
150
analysis time
HDL_C = low_HDL
HDL_C = high_HDL

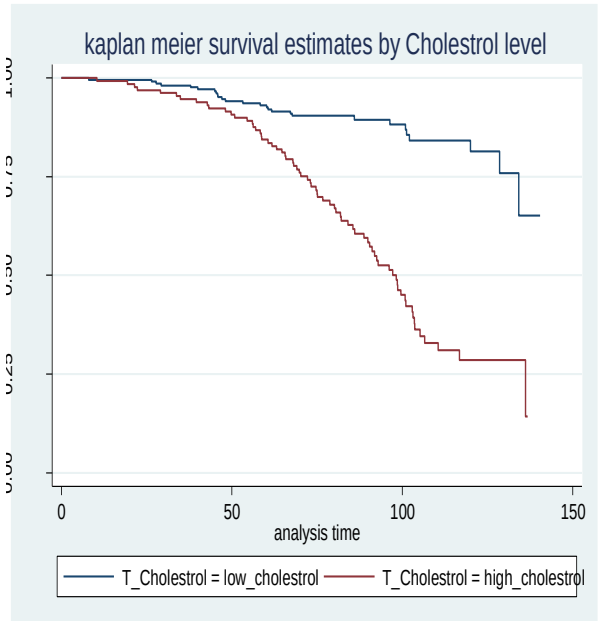
I


kaplan meier survival estimates by LDL-C level
0.00
0.25
0.50
0.75
1.00
0
50
100
150
analysis time
LDL_C = Low_LDL
LDL_C = high_LDLI

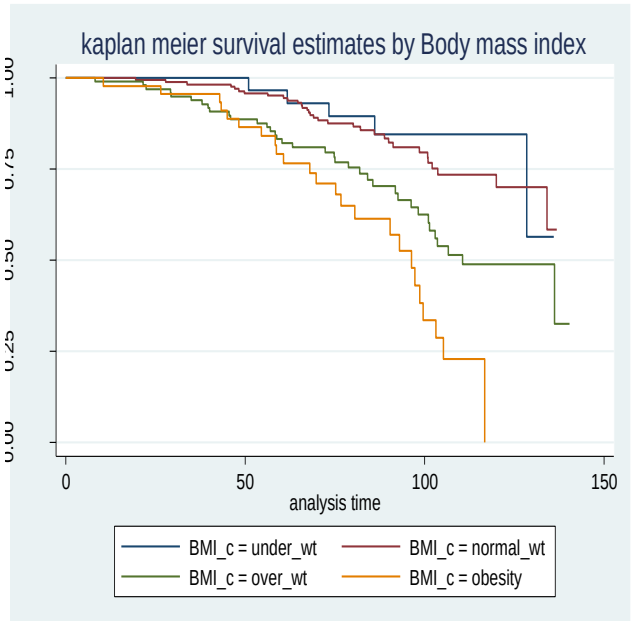
J


kaplan meier survival estimates by Triglyceride level
0.00
0.25
0.50
0.75
1.00
0
50
100
150
analysis time
Triglycerid = low_trigliceride
Triglycerid = high_triglyceride

K.


kaplan meier survival estimates by Cholestrol level
0.00
0.25
0.50
0.75
1.00
0
50
100
150
analysis time
T_Cholestrol = low_cholestrol
T_Cholestrol = high_cholestrol

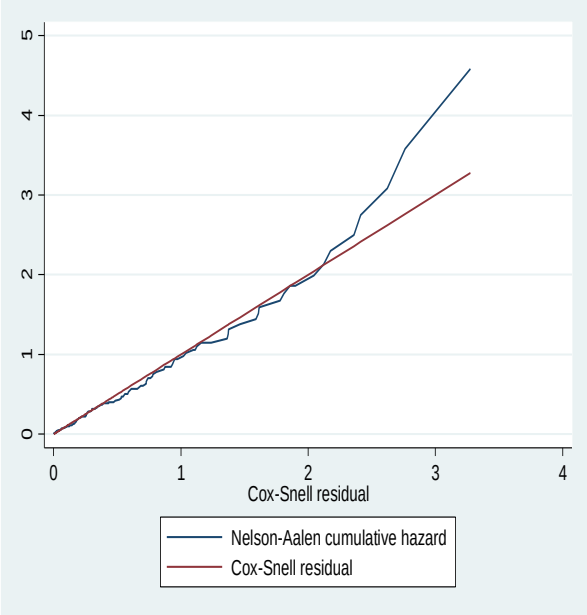
L.


kaplan meier survival estimates by Body mass index
0.00
0.25
0.50
0.75
1.00
0
50
100
150
analysis time
BMI_c = under_wt
BMI_c = normal_wt
BMI_c = over_wt
BMI_c = obesity

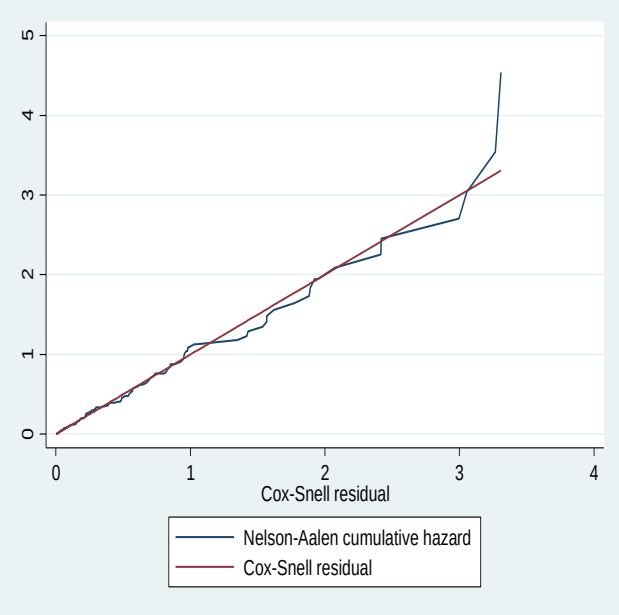
Appendix 5

Figure: Cox-Snell residuals obtained by fitting exponential, Weibull and Gompertz models for type II DM patients under ant diabetic's treatment in University of Gondar Referral hospital September, 2005 – August, 2012

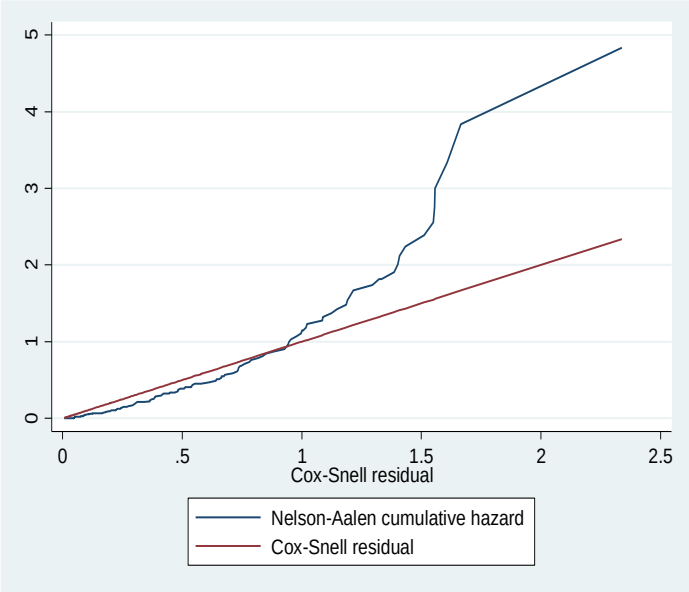
A. Weibull



B. Gompertz



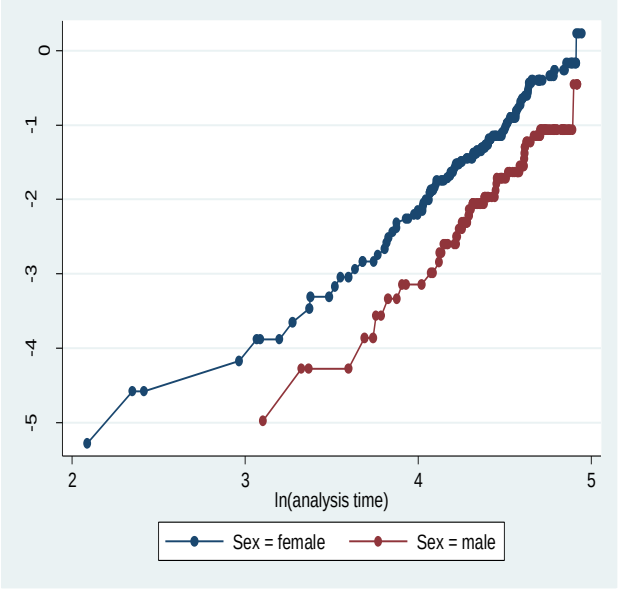
C. Exponential

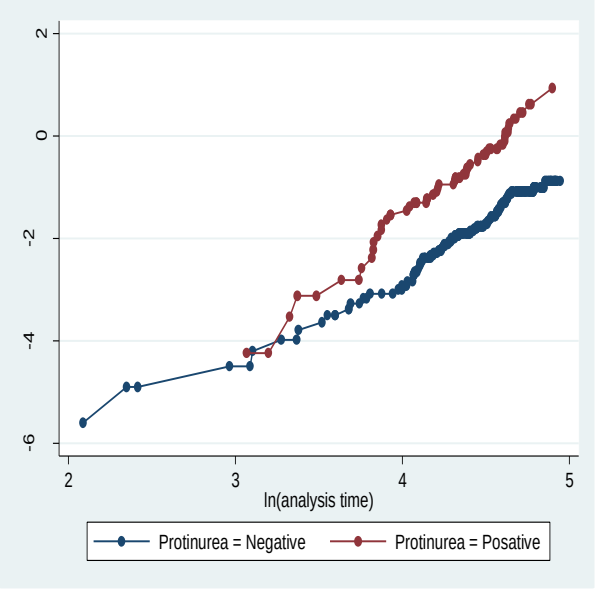


Appendix 6

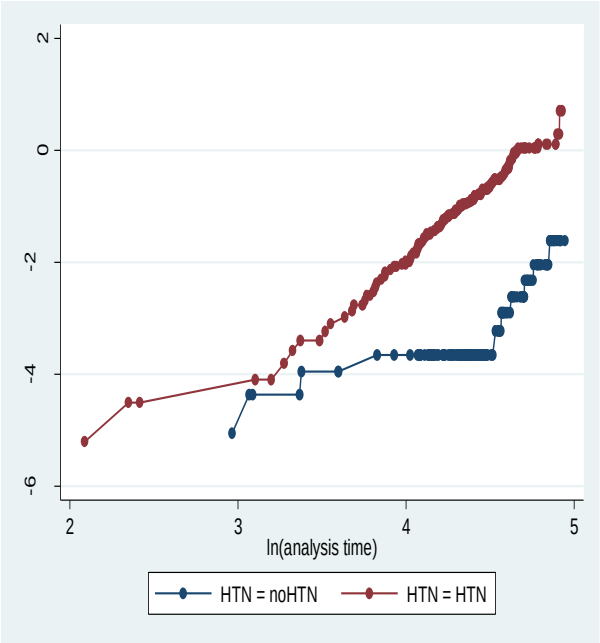
Figure: –log(log(Survival probability) VS log (Survival time) plot for different categorical covariates among type II DM patients in university of Gondar referral hospital September 2005- August 2012.

A. **B.**

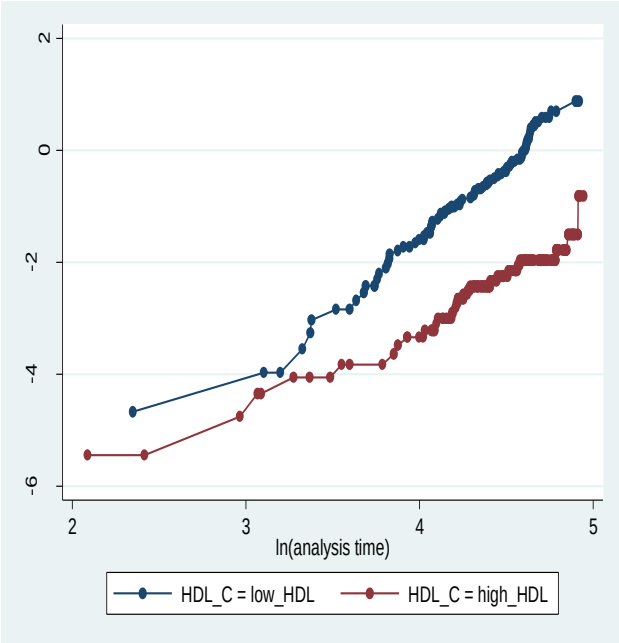




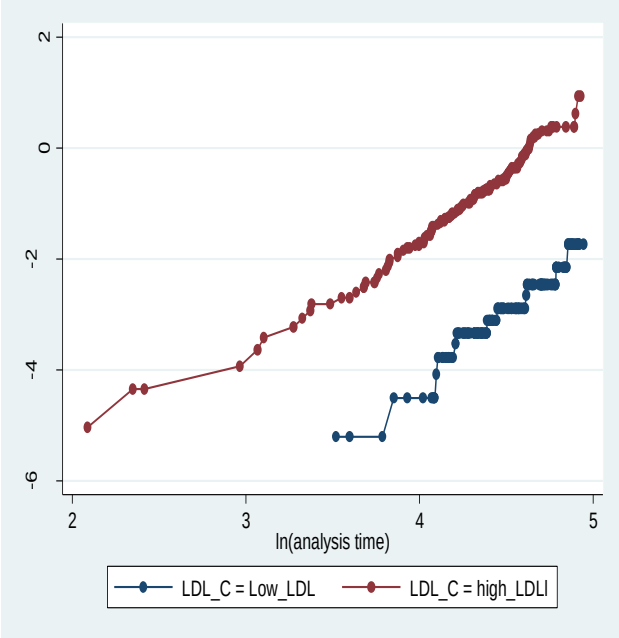
C **D.**

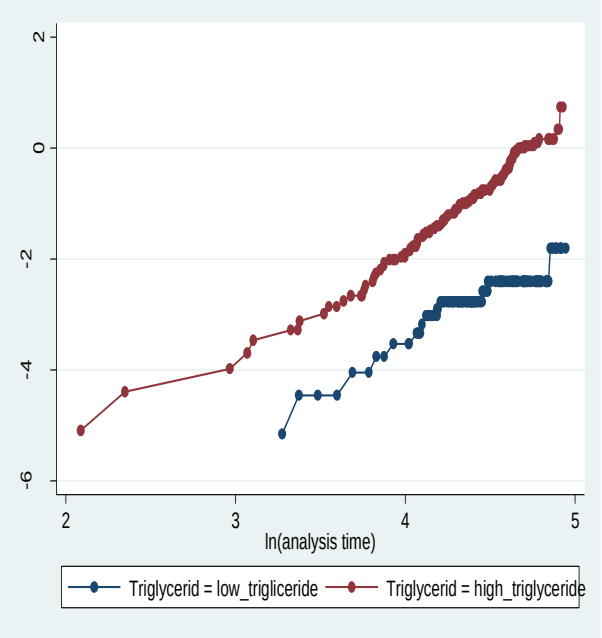

2
0
-2
-4
-6
2
3
4
5
ln(analysis time)
HTN = noHTN
HTN = HTN

E.

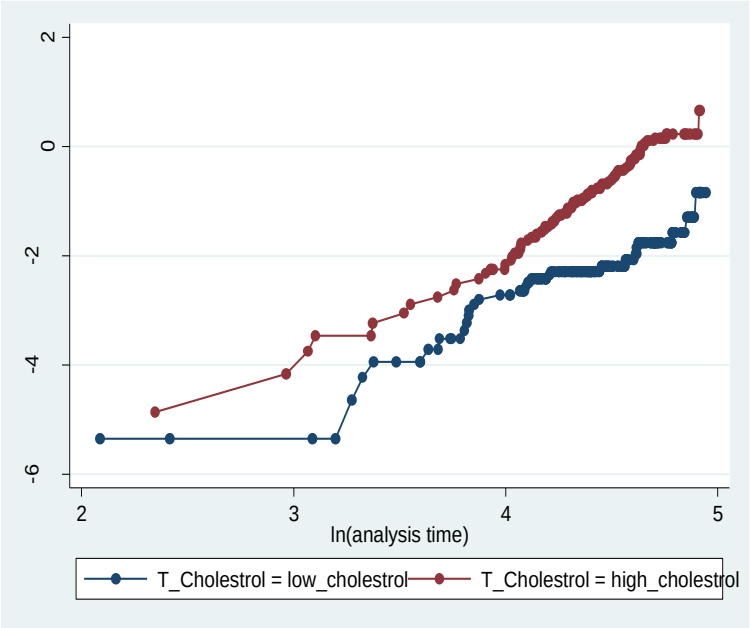

2
0
-2
-4
-6
2
3
4
5
ln(analysis time)
HDL_C = low_HDL
HDL_C = high_HDL

F.


2
0
-2
-4
-6
2
3
4
5
ln(analysis time)
LDL_C = Low_LDL
LDL_C = high_LDLl


2
0
-2
-4
-6
2
3
4
5
ln(analysis time)
Triglycerid = low_trigliceride
Triglycerid = high_triglyceride

G



Declaration

I, the undersigned, senior MPH student declare that this thesis report is my original work in partial fulfillment of the requirement for the degree of Master of Public Health in Biostatistics.

Name: Haileab Fekadu
Signature: _____

Place of submission: Institute of public Health, College of Medicine and Health Sciences, University of Gondar.

Date of Submission: _____

This thesis report has been submitted for ethical evaluation with our approval as university advisor(s).

Advisors

Name	Signature
1. Dr. Asrat Atsedewyen	----------
2. Mr Adissu Jember	----------

ASSURANCE OF INVESTIGATOR

I, the undersigned, senior MPH student agree to accept responsibility for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as pre terms and conditions of the research and publications office of the University of Gondar.

Name of the student: Haileab Fekadu

Date: _____ Signature: _____

Approval of the advisor (s)

Advisors

Name	Signature	Date

1. Dr. Asrat Atsedeweyen _____ _____
2. Mr Adissu Jember _____ _____